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ALDH1A1 and ALDH3A1 Expression of Melanocytic Neoplasms and Associated with Clinicopathological Parameters in Chinese People

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Background: ALDH1A1 and ALDH3A1 were reported to be highly expressed in some cancerous tissues. The aim of this study was to assess ALDH1A1 and ALDH3A1 expression and cellular localization in a spectrum of melanocytic lesions, ranging from common melanocytic nevi (CMN) and dysplastic nevi (DN) to acral melanoma (AM). We also compared the clinicopathological correlation of AM in a large Chinese population. **Material and Methods:** We used purified class-specific antibodies against ALDH1A1 and ALDH3A1 to elucidate the cellular distribution of these proteins in a human tissue microarray derived from 20 patients with CMN, 12 patients with DN, and 80 patients with primary acral MM. The cytoplasmic immunostaining score was obtained by multiplying the percentage of antigen-positive cells by their average immunostaining intensity. Mean±S.E.M. for each experimental group was calculated and compared. The relationships between AJCC TNM stage and cytoplasmic scores of ALDH1A1 and ALDH3A1 were examined. **Results:** A statistically higher score for ALDH1A1 staining was noted in CMN than in DN ($p < 0.028$). ALDH3A1 staining was significantly different between CMN and AM. No statistical differences in survival and no association between cytoplasmic staining of both enzymes and other clinical parameters were demonstrated. **Conclusion:** ALDH1A1 and ALDH3A1 were differentially expressed in CMN, DN, and AM; yet, these enzymes may not be appropriate for use as prognostic factors.

Key Words: ALDH1A1, ALDH3A1, melanocytic neoplasms

INTRODUCTION

Malignant melanoma (MM), arising in cutaneous melanocytes, is the most aggressive form of skin cancer. However, MM is notoriously resistant to conventional chemotherapy, and the persistent lack of effective treatment modalities creates an urgent need for novel pharmacological agents for use in MM therapy.[1]

Cancer cell metabolism is an old pathogenetic issue that has recently gained new interest as a target for therapeutic approaches.[2-3] Recently, the expression and the activity of aldehyde dehydrogenases (ALDHs) were found in MM.[4] Other studies have also implied that ALDH isozymes are not only biomarkers of cancer stem cells, but are also attractive therapeutic targets for human melanoma.[5]

The superfamily of ALDHs is involved in cellular homeostasis by metabolizing both endogenous and exogenous reactive compounds.[6-7] In addition, they also modulate several cell functions, including proliferation, differentiation, and survival, as well as the cellular response to oxidative stress. Class I aldehyde dehydrogenase A1 (ALDH1A1), also known as retinaldehyde dehydrogenase 1 (RALDH1), oxidizes all-trans retinaldehyde to all-trans retinoic acid (ATRA) in an irreversible reaction.[8] ALDH3A1, one of the ALDH3 family of isozymes, has the ability to protect tissue against UV light-induced damage.[9] It is hypothesized that this protective function of ALDH3A1 could involve removal of toxic aldehydes formed during UV-induced lipid peroxidation.[10]

Oxidative stress, accompanied by lipid peroxidation

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(LPO), leads to generation of a variety of products, such as a highly reactive aldehyde 4-hydroxynonenal (4-HNE) which induces covalent modification of proteins and DNA. Several studies have determined that ALDH1A1 and ALDH3A1 can catalyze the detoxification of 4-HNE by converting it to 4-HNE.[10-13] Some studies have also found that melanoma cells have a decreased ability to handle oxidative stress as compared to melanocytes and structurally abnormal melanosomes that generate free radicals.[14-16]

Interestingly, several studies have determined that overexpression of ALDH1A1 and ALDH3A1 in cell lines confers resistance to oxazaphosphorines, including cyclophosphamide and its metabolites.[17-18] It is worth noting that disulfiram (DSF), one of the potent inhibitors of ALDH1A1 and ALDH3A1, has been reported to decrease cellular proliferation and to induce apoptosis in human melanoma cells.[19-20]

To date, no clear relationship between the expression of ALDH1A1 and ALDH3A1 and melanocytic neoplasms has been established in Chinese people. Because of the possible involvement of these two enzymes in the cancer metabolism in MM, we tested the immunohistochemical expression of ALDH1A1 and ALDH3A1 in a spectrum of melanocytic lesions, ranging from common melanocytic nevi (CMN, including junctional nevi, intradermal nevi, and compound nevi) and dysplastic nevi (DN) to acral melanoma (AM). We also examined the clinicopathological correlations of MM with ALDH1A1 and ALDH3A1 expression in a large Chinese population.

MATERIALS AND METHODS

Human Subjects

Formalin-fixed, paraffin-embedded samples from 40 patients with CMN, 24 patients with DN, and 111 patients with primary and/or secondary MM were archived in the Department of Pathology at Tri-Service General Hospital, Taipei, Taiwan, between 1986 and 2005 and were used in this study. After approval of the study protocol by the Hospital Review Board (TSGHIRB 098-05-058) and excluding patients for whom the necessary clinical information was lacking (e.g., age, gender, lesion location, or Tumor Node Metastasis [TNM] stage), 20 patients with CMN, 12 patients with DN, and 80 patients with primary acral MM were included in our research.

Preparation of Tissue Microarray

We collected 863 tissue blocks for sectioning and initial microscopic evaluation; 245 representative blocks were selected for construction of tissue microarrays after review of the initial H&E-stained sections. Clinical staging was based on the 2006 AJCC/TNM system. We obtained 2-3 cores for each case of CMN and DN, and 3-6 cores for each primary and secondary melanoma, from different selected areas of the tissue blocks, to construct tissue microarray slides. Each representative core in the tissue microarray slide was 1.5 mm in diameter. All the slides were reviewed by two experienced dermatopathologists (HWG and BYW) to verify the histological diagnosis.

Generation and Purification of Antibodies

Rabbit antisera against human ALDH1A1 and ALDH3A1 were produced from our laboratory, using methodology described earlier.[21] Class cross-reactivity of the polyclonal antisera was eliminated by affinity chromatography using sepharose covalently linked to the respective non-immunogen isozymes, i.e., the ALDH family members that were not used for immunization, according to the manufacturer's recommendations. The class-specific antibodies so obtained were then further purified by affinity chromatography using the antigen isozymes, i.e., ALDH1A1, ALDH2, or ALDH3A1, immobilized on the sepharose resins. The affinity-purified antibodies, in phosphate-buffered saline (PBS) containing 5% BSA, remained stable for at least 3 months when stored in aliquots at -70°C. Concentration of the affinity-purified antibodies was assessed by an enzyme-linked immunosorbent assay with a commercially available rabbit IgG standard, as described previously.[22]

Immunohistochemistry

Tissue microarray slides were dewaxed in xylene, rehydrated in alcohol, and immersed in 3% hydrogen peroxide for 5 min to suppress endogenous peroxidase activity. Antigen retrieval was performed by heating (100°C) each section for 30 min in 0.01 mol/L sodium citrate buffer (pH 6.0). After three rinses (for 5 min in PBS, each time), sections were incubated for 1 h at room temperature with purified anti-ALDH1A1 and ALDH3A1 antibodies, all diluted in PBS. After three washes (for 5 min, each time) in PBS, sections were incubated with biotin-labeled secondary immunoglobulin (1:100; DAKO, Glostrup, Denmark) for 1 h at room temperature. After three additional washes, peroxidase activity was developed with the AEC chromogen system (DAKO) at room temperature.

Evaluation of Immunoreactivity

Cytoplasmic immunostaining intensity was assessed for ALDH1A1 and ALDH3A1, using a scale of 0 (no staining) to 4 (strongest). Additionally, the percentage of tumor cells at each immunostaining intensity was calculated. The cytoplasmic immunostaining score was obtained by multiplying the percentage of antigen-positive cells by their average immunostaining intensity and ranged from 0 to 400.

Statistical analysis

All results of cytoplasmic staining scores are presented as the mean ± standard error of the mean (S.E.M.). Fisher's exact test and Student's t-test were applied in statistical analysis among the groups. A p-value < 0.05 was considered to be statistically significant. Survival time was defined as the period from the date of histological diagnosis to the date of death due to melanoma, based on the records retrieved from the Cancer Committee and Center for Cancer Prevention of Tri-Service General Hospital, Taipei, Taiwan. The Kaplan-Meier survival test was used in statistical analysis of survival time. SigmaPlot, and SigmaStat software (Jandel Scientific, San Rafael, CA, USA) were used to perform linear regression testing, and the Pearson Product Method correlation was used to analyze the relationship between immunohistochemical expression and clinicopathologic parameters.

RESULTS

Clinical profiles

Clinicopathological features of CMN, DN, and MM are summarized in Table 1. All patients included in our study are ethnic Chinese residents of Taiwan. The median age at diagnosis of CMN and DN patients was 48 y (range: 32-73 y) and 30 y (range: 20-59 y), respectively. The median age of AM patients was 41 y (range: 16-81 y). AM, by definition, involved acral regions. The percentage of lesions of CMN and DN at acral sites was 45% and 50%, respectively. Additionally, from a histopathological point of view, no phenotypic differences in CMN/DN were noted for acral or non-acral sites.

Cytoplasmic Expression of ALDH1A1 and ALDH3A1

Representative sections of CMN, DN, and MM, immunostained for ALDH1A1 and ALDH3A1, are shown in parallel with adjacent H&E-stained sections in Fig. 1. The results of cytoplasmic immunostaining for ALDH1A1 and ALDH3A1 in CMN, DN, and AM are presented in Table 1.

Statistically higher scores for ALDH1A1 staining were noted in CMN (Fig. 1D, Table 1) than in either DN (Fig. 1E, Table 1) or AM (Fig. 1F, Table1). However, only the difference between CMN and DN was statistically significant (p < 0.028). Cytoplasmic ALDH1A1 immunoreactivity was also found in eccrine ducts and suprabasal keratinocytes (Fig. 1E).

Cytoplasmic ALDH3A1 staining was not significantly different among CMN (Fig. 1G, Table 1), DN (Fig. 1H, Table 1), and AM (Fig. 1I, Table 1; p > 0.05). Cytoplasmic and nuclear ALDH3A1 staining was mainly found in basal keratinocytes (Fig. 1H).

Table 1 Clinical profiles and cytoplasmic immunostaining scores of ALDH1A1 and ALDH3A1 in common melanocytic nevi (CMN), dysplastic nevi (DN) and acral melanoma (AM).

	Sample Numbers	Sex (M:F)	Age Median years (range)	ALDH1A1 Score	ALDH3A1 Score
CMN	20	9:11	41 (6-81)	139.25 ± 12.33	129.7 ± 12.53
DN	12	7:5	30 (20-59)	5.83 ± 11.087*	127.83 ± 13.00
AM	80	46:34	41 (16-81)	126 ± 13.31	162.55 ± 14.07#

M, male; F, female. Data are mean ± standard error of the mean (S.E.M.) of immunostaining scores for ALDH1A1 and ALDH3A1 in common melanocytic nevi, dysplastic nevi and acral melanoma.
* p < 0.05 for DN versus CMN comparison.
# p < 0.05 for AM versus CMN comparison.

Clinicopathological analysis

Analysis of overall survival for immunostaining scores of AM is shown in Fig. 2A (ALDH1A1) and Fig. 2B (ALDH3A1). The relationships between AJCC TNM stage and cytoplasmic scores of ALDH1A1 and ALDH3A1 are presented in Fig. 3 and Fig. 4, respectively.

No significant difference in survival was seen when the data were analyzed for cytoplasmic immunoreactivity scores of ALDH1A1 and ALDH3A1 in AM (Fig. 2A and 2B). No association was demonstrated between cytoplasmic staining of ALDH1A1 and ALDH3A1 positivity and other clinical parameters, including age, gender, tumor location, invasion depth, tumor ulceration, and AJCC stage of AM after adjusting for T stage.

DISCUSSION

In this study, we established that ALDH1A1 and ALDH3A1 were differentially expressed in human common

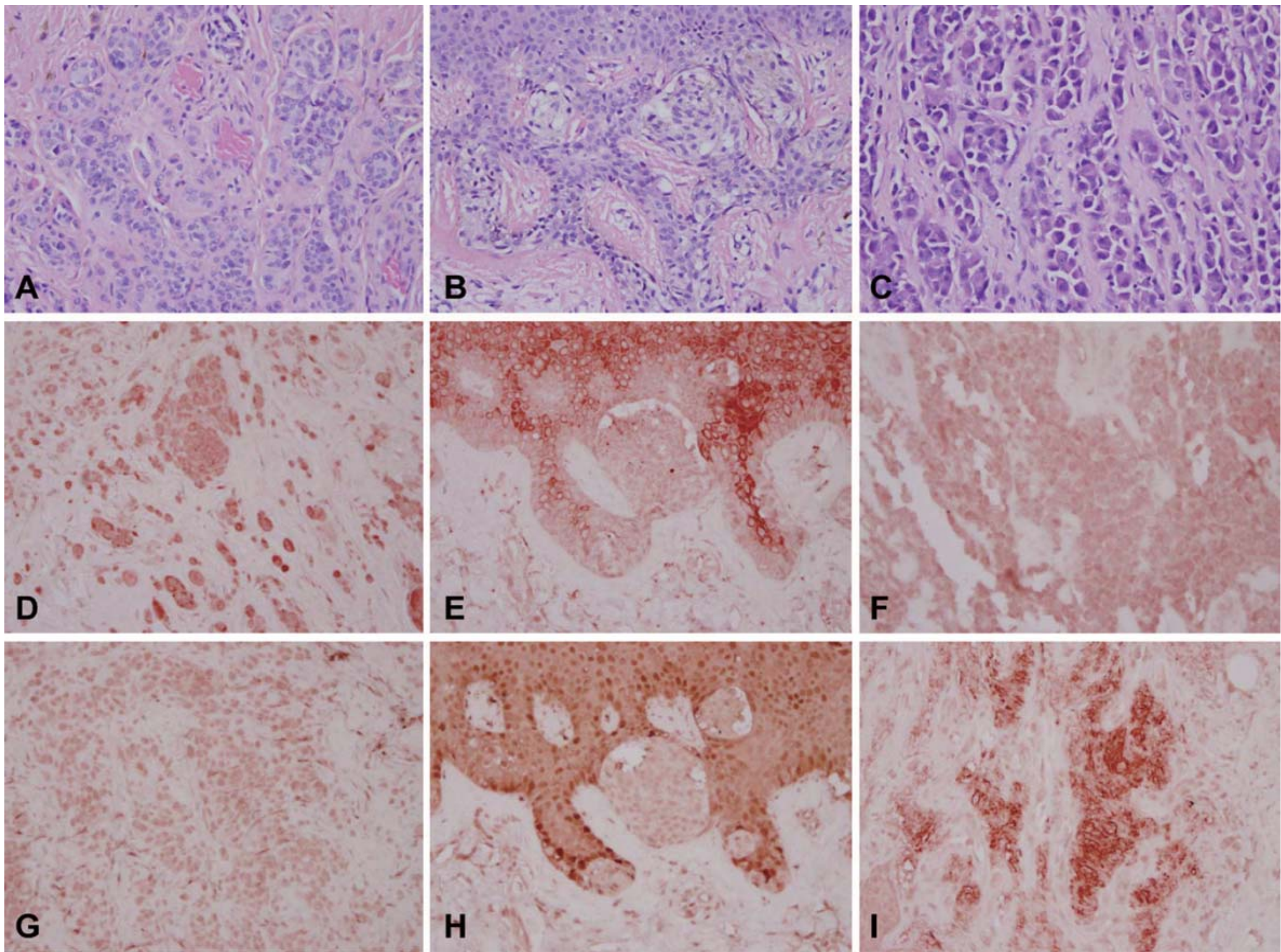

Fig. 1 Representative microphotographs of H&E staining and cytoplasmic immunohistochemical profiles of CMN (A, D, G), DN (B, E, H), and overall melanoma (MM) (C, F, I). D-F, ALDH1A1 staining: higher cytoplasmic ALDH1A1 score in CMN (D) than in DN (E) or in melanoma (F); G-I, ALDH3A1 staining: strong cytoplasmic expression in CMN (G), DN (H), and melanoma (I) without significant difference. (Original magnification, 400×)

melanocytic nevi, dysplastic nevi, and malignant melanoma. Significant changes in cytoplasmic ALDH1A1 immunohistochemical scores were noted between CMN and DN. ALDH1A1 plays pleiotropic roles in UV-radiation resistance melanogenesis and stem cell maintenance, by catalyzing the conversion of lipid aldehydes to a lipid carboxylic acid, 9-cis retinoic acid.[8,23-24] Thus, we suggest that in DN the ability to oxidize retinaldehyde to retinoic acid via ALDH1A1 may be less functional than in CMN, due to the poor differentiation of DN. Although no significant changes in the cytoplasmic ALDH1A1 immunohistochemical scores between CMN or DN and AM were observed, the scores in AM was higher than those in DN. This reversal of scores could be supported by a previous report that ALDH1A1 could be a marker of human melanoma stem cells.[5] In fact, ALDH1A1 was also proven to be a cancer stem cell marker in lung cancer, squamous cell carcinoma of the head and neck, and colon cancer.[4,25-27] Previous reports found that ALDH1A1-positive melanoma cells are more resistant to chemotherapeutic agents and that silencing ALDH1A leads to cell cycle arrest and apoptosis.[5] This result further supports the proposal that most AM develops de novo[28]; we further suggest that AM might derive from melanoma cancer stem cells, and not directly from DN. No further statistically significant associations between cytoplasmic immunostaining scores of ALDH1A1 and TNM stage and survival of AM were identified. The data revealed that ALDH1A1 expression may be an early event in the course of melanoma cancer stem cell formation and that this protein may be less in-

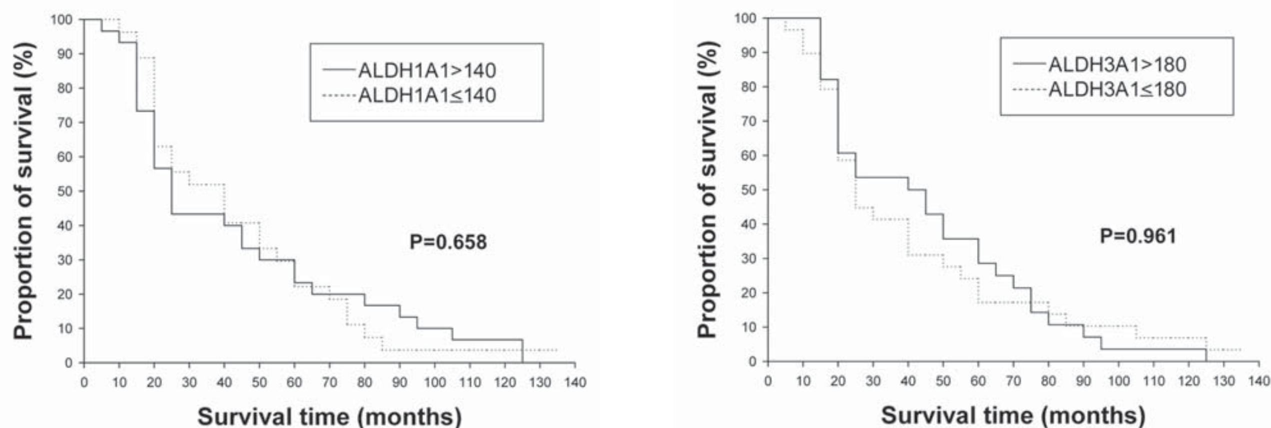

Fig. 2 (A, B) Survival analysis of AM for cytoplasmic immunostaining scores of ALDH1A1(2A), ALDH3A1(2B). There is no significant correlation between survival rate and cytoplasmic immunostaining score in the analyses. Patients were divided into two groups (high vs. low scores) for each analysis at the median staining intensity score. Survival rates were analyzed using the Kaplan-Meier survival test.

volved in subsequent tumor progression and metastasis.

In this study, we observed a significant difference in the ALDH3A1 immunohistochemical scores between CMN and AM. This result implies that oxidative stress and lipid peroxidation may be more prominent during development of melanoma and that these events then induce the detoxification function of ALDH3A1 in melanoma. ALDH3A1 can catalyze the oxidation of medium-chain length aliphatic aldehydes to carboxylic acids.[29] During tissue damage, the lipid peroxidation formed the metabolic toxic aldehydes, such as HNE and MDA (malondialdehyde); these toxic metabolites cause protein damage, growth inhibition, and apoptosis.[30-32] Thus, it may be reasonable to suppose that attenuated ALDH3A1 expression may impair the ability to eliminate toxic aldehydes under conditions of oxidative stress. Nevertheless, there were no statistically significant associations between cytoplasmic ALDH3A1 immunostaining scores and TNM stage and survival in AM patients. ALDH3A1 may also be less associated with tumor progression and metastasis than ALDH1A1, but was expressed under oxidative stress. Hence, both ALDH1A1 and ALDH3A1 could play potential roles in the cutaneous melanocytic lesions, such as CMN, DN, and melanoma. In support of this proposal, a clinical trial has indicated that DSF, the inhibitor of ADLH1A1 and ALDH3A1, may potentiate the anti-cancer effects of some chemotherapeutic agents.[33] In addition, DSF is currently being tested in patients with metastatic melanoma.[34]

In conclusion, our study demonstrated for the first time that changes in the cytoplasmic levels of ALDH1A1 and ALDH3A1 may be an early event, which includes tumor initiation and proliferation in melanoma pathogenesis, and we suggest that both enzymes could be biomarkers for early detection of melanoma. In contrast, these two proteins could be less involved in later events which consist of tumor aggression and ability to metastasis. However, the relationship between the early and late course of the disease is continuous with different biologic events and molecular changes.[35] Further investigation of these proteins would extend our understanding of the underlying molecular mechanisms and could lead to the development of pharmacologic agents that could prolong the survival of patients with melanoma.

DISCLOSURE

All authors declare no competing financial interests.

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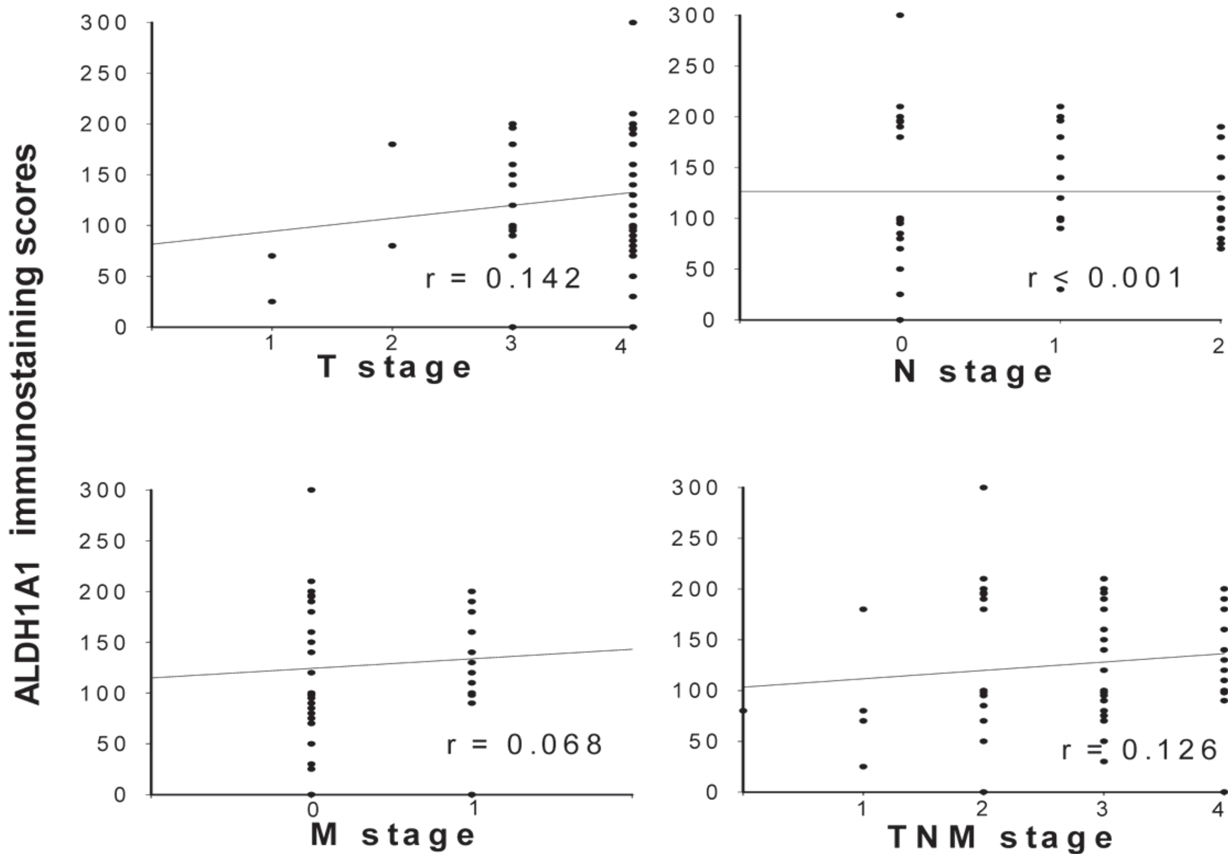

Fig. 3 Clinicopathologic correlations with the cytoplasmic immunoreactivity scores of ALDH1A1 in overall melanomas. There is no statistical significance by linear regression testing.

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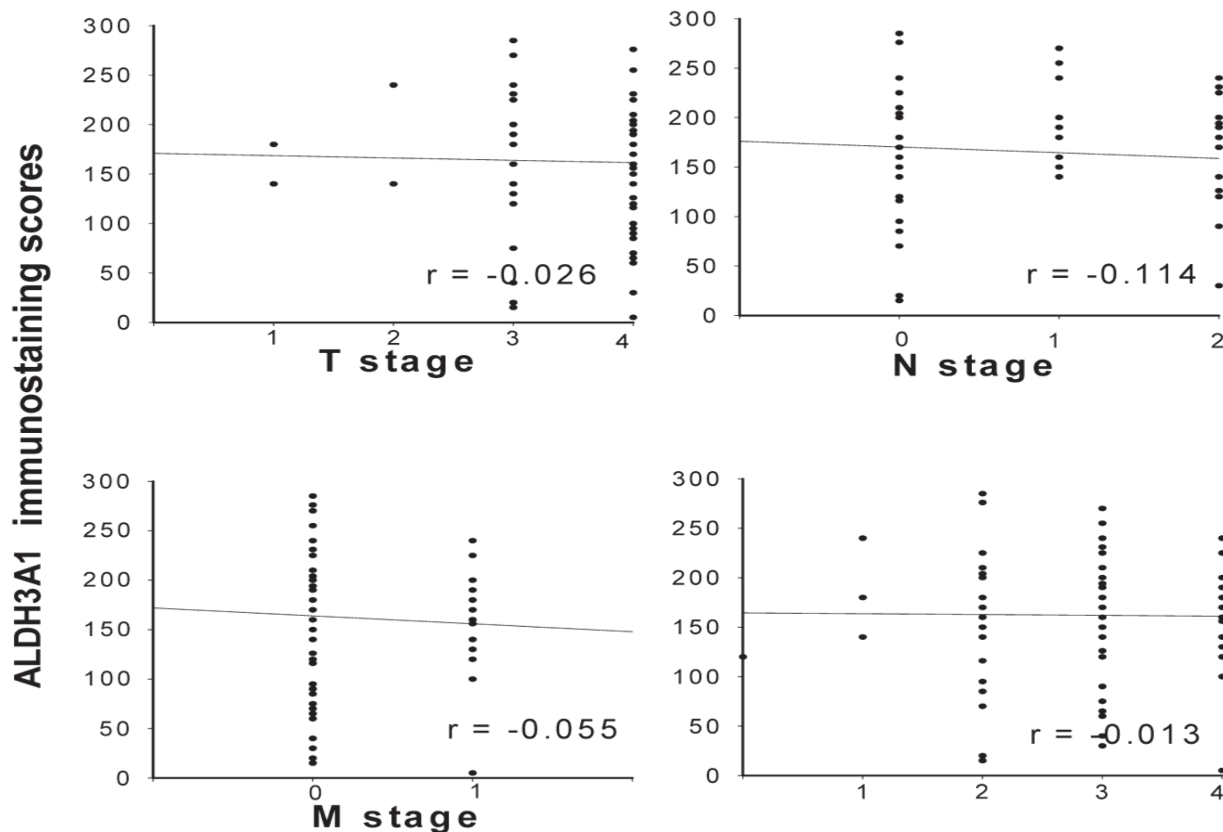

Fig. 4 Clinicopathologic correlations with the cytoplasmic immunoreactivity scores of ALDH3A1 in overall melanomas. There is no statistical significance by linear regression testing.

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