Immunohistochemical CD10 Expression is Useful for Differentiating Malignant Melanoma from Benign Melanocytic Nevus

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Abstract

Malignant melanoma (MM), an aggressive skin neoplasm, can be difficult to differentiate histologically from benign melanocytic nevi (BMN). Although immunohistochemical analysis could facilitate diagnosis of MM, markers that discriminate between benign and malignant lesions have not yet been established. However, CD10 expression is associated with MM progression. We immunostained 36 MM and 50 BMN specimens for CD10 to evaluate whether CD10 immunostaining could distinguish between BMN and MM tumors. In the 36 MM samples, we found CD10 expression in 17 (47.2%) sample tumor cells and 32 (88.9%) stromal cells, for 34 of the 36 MM specimens (94.4%) overall. In contrast, no BMN (0/50) samples had CD10⁺ tumor cells, although a few (8/50, 16.0%) showed stromal staining. The two specimen types thus significantly differed in CD10 expression ($P < 0.01$), indicating that melanocytic CD10⁺ tumor cells are likely to be malignant. Also, melanocytic stromal cells with diffuse, strong CD10 expression are more likely to be malignant than those with light, focal CD10 expression. Although hematoxylin and eosin staining is fundamental to the diagnosis of melanocytic lesions, CD10 immunostaining may help distinguish between BMN and MM.

Key words

CD10, immunohistochemistry, malignant melanoma, melanocytic nevus

Introduction

Malignant melanoma (MM), an aggressive skin neoplasm with poor prognosis, is diagnosed by clinical and pathological findings. In the clinical arm, use of dermatoscopy to diagnose MM has improved in recent years^{1,2}. Similarly, immunohistochemistry (IHC) and molecular analyses are the leading developments in pathological diagnosis. However, histopathological diagnoses of melanocytic lesions are occasionally challenging. Although clearly aggressive MMs can be diagnosed without difficulty, MMs with equivocal invasiveness, such as *in situ* lesions, or those with similar morphology to melanocytic nevi (BMN) are often problematic. IHC is a useful tool, but diagnostic panels for differentiating MM from

BMN are controversial^{3–5}. Representative melanocytic markers, including S100, HMB-45, and melan-A, are often used in diagnosing melanocytic lesions; although they are useful for MM and tumors with melanocytic differentiation³, their use in distinguishing malignant and benign melanocytic lesions is limited³.

CD10 expression can reportedly predict aggressiveness of MM^{6–9}. CD10 is a cell surface glycoprotein expressed in both normal and neoplastic cells, including follicular lymphoma¹⁰, renal cell carcinoma¹¹, endometrial stromal sarcoma^{11,12}, atypical fibroxanthoma¹³, and many benign or malignant tumors^{11,13}, although the precise function of CD10 in each tumor is still not fully understood¹⁴.

CD10 expression in MM was first described by

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Jongeneel et al.¹⁵⁾ using flow cytometry in cell lines. Carrel et al.¹⁶⁾¹⁷⁾ then showed CD10 expression *in vivo* in MM tissues by IHC; several other reports have significantly correlated CD10 expression levels with tumor progression^{6)8)18–20)}.

Although a number of studies have shown CD10 expression in MM, very little is known about its expression in melanocytic nevus, a benign counterpart of MM²⁰⁾. In this study, we compared IHC expression patterns of CD10 in MM and melanocytic nevus and examined the usefulness of CD10 in differential diagnosis of these lesions.

Materials and methods

We retrieved specimens from the pathology database in St. Marianna University Hospital, all of which were fixed with formalin and embedded in paraffin. We selected typical BMN specimens with wide dermal spreading (i.e. intradermal or compound type, $n=50$) and cutaneous MM with unequivocal dermal invasion ($n=36$). Morphological diagnoses of these lesions were confirmed by at least two pathologists.

We performed IHC staining on 3- μ m-thick paraffin sections. Melanin bleaching with warm diluted hydrogen peroxidase was performed on some samples with massive pigmentation²¹⁾. Sections were incubated for 2 hours at room temperature with a monoclonal mouse anti-human CD10 antibody (clone: 56C6, 1:2 dilution, Nichirei, Tokyo). Reacted antibodies were detected by Simple Stain MAX-PO (Nichirei, Tokyo, Japan). We scored CD10 expression as 3+: $\geq 50\%$ of tumor cells CD10⁺; 2+: 10–50% of tumor cells CD10⁺; and 1+: $< 10\%$ of tumor cells CD10⁺. In stromal cells, CD10 expression was evaluated as diffuse, focal, or negative. We analyzed correlation of CD10 expression between MM and BMN using Fischer's exact test. $P < 0.05$ was considered to be significant. We also analyzed sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of CD10 expression in MM and BMN, as described elsewhere⁶⁾²²⁾.

This study was approved by the Institutional Ethics Committee of St. Marianna University School of Medicine (approval no. 2797).

Results

The 36 patients with MM ranged in age from 4 to 89 years old (63.8 ± 17.7 , mean $\pm$ S.D). Their MM subtypes were 12 cases (33.3%) of acral lentiginous melanoma; 19 (52.8%) of nodular melanoma; and 5 (13.9%) of superficial spreading melanoma (Table

1). The 50 patients with BMN ranged in age from 7 to 75 years (41.1 ± 16.6).

Morphologically, representative MM cells had pleomorphic and eosinophilic cytoplasm and oval-shaped nuclei with prominent nucleoli (Fig. 1a), whereas BMN were composed of relatively monotonous small round cells with fine nuclei. No maturation was seen in MM, but typical BMN cells showed maturation according to the depth of dermis.

Among the tumor cells in the 36 MM samples, 17 were CD10⁺ (47.2%; Fig. 1 b–d), whereas all 50 BMN samples were CD10[−] ($P < 0.01$; Table 2; Figures 1 and 2). Of these 17 MM samples with CD10⁺ tumor cells, 6 scored 3+ (16.7%, Fig. 1b); 5 scored 2+ (13.9%, Fig. 1c); and 6 scored 1+ (16.7%, Fig. 1d). We also found CD10 expression in stromal cells in 32 of 36 MMs (88.9%, Fig. 1f, h), with intratumoral spreading in 4 cases (11.1%; intratumoral pattern, Fig. 1e, f), peritumoral proliferation in 16 cases (44.4% peritumoral pattern, Fig. 1g, h); and combined intra- and peritumoral patterns in 12 cases (33.3%). In contrast, stromal cells in only 8 of 50 BMN samples expressed CD10 (16.0%), all in intratumoral patterns (Figure 2); six had CD10⁺ stromal cells located near deep dermal vessels (Fig. 2a, b), one had CD10⁺ stromal cells widely spread from the hair follicles and vessels (Fig. 2c, d), and the remaining case had relatively diffuse CD10⁺ stromal expression through the lesion. This last case was associated with a skin ulcer and infiltration of CD10⁺ granulocytes (Fig. 2e, f). In BMN, CD10⁺ stromal cells were focal and thin or fine in nevi compared with a diffuse, thick pattern in MMs.

The CD10⁺ tumor and stromal cells combined marked 34 MM cases (94.4%), compared with 8 BMN cases (16.0%; $P < 0.01$). In MM tumor cells, this method was 47% sensitive, 100% specific with 100% PPV and 73% NPV (Table 3), but 0% sensitive, 53% specific, with 0% PPV and 28% NPV for BMN tumor cells. For CD10⁺ tumor and stromal cells combined, results were 94% sensitive and 84% specific with 81% PPV and 96% NPV for MM, and 16% sensitive and 6% specific with 19% PPV and 5% NPV for BMN.

Discussion

Invasive MM is an aggressive skin neoplasm that shows downward dermal infiltration with destruction of skin appendages, vessels, and interstitial stromal fibroblasts, whereas BMN may spread in the dermis without destruction of dermal structures. Al-

Table 1. Clinicopathological Features of Patients with Nevus or Melanoma

		Melanoma	Nevus
Sex	Male	19 (52.8%)	19 (38.0%)
	Female	17 (47.2%)	38 (76.0%)
Age (years)	Range	4–89	7–75
	Mean $\pm$ SD	63.8 $\pm$ 17.7*	41.1 $\pm$ 16.6*
Site	Head and neck	4 (11.1%)	38 (76.0%)
	Trunk	3 (8.3%)	11 (22.0%)
	Genital area	4 (11.1%)	0 (0%)
	Extremity	25 (69.4%)	1 (2%)
Subtype	ALM	12 (33.3%)	n/a
	NM	19 (52.8%)	n/a
	SSM	5 (13.9%)	n/a
Clark level	II	1 (2.8%)	n/a
	III	9 (25.0%)	n/a
	IV	20 (55.6%)	n/a
	V	6 (16.7%)	n/a
Thickness (mm)*	Range	1.0–13.0	1.2–6.7
	Mean $\pm$ SD	4.3 $\pm$ 2.7	3.0 $\pm$ 1.1

ALM: acral lentiginous melanoma; MM: malignant melanoma; n/a: not applicable; NM: nodular melanoma; SSM: superficial spreading melanoma.

*Thickness refers to Breslow's scale and is also applied to nevi.

Table 2. Results of Immunohistochemistry for CD10 in Tumor and/or Stromal Cells

		MM	Nevus	Total	p-value
Tumor cells					
	CD10+ total	17 (47.2%)	0 (0%)	17	
	3+	6 (16.7%)	0 (0%)		
	2+	5 (13.9%)	0 (0%)		
	1+	6 (16.7%)	0 (0%)		
	CD10-	19 (52.7%)	50 (100%)	69	<0.01*
Stromal cells					
	CD10+ total	32 (88.9%)	8 (16.0%)	40	
	intratumoral pattern	4 (11.1%)	8 (16.0%)		
	peritumoral pattern	16 (44.4%)	0 (0%)		
	both patterns	12 (33.3%)	0 (0%)		
	CD10-	4 (11.1%)	42 (84.0%)	46	<0.01*
Either tumor or stromal cells					
	CD10+	34 (94.4%)	8 (16.0%)	42	
	CD10-	2 (0.05%)	42 (84.0%)	44	<0.01*

*Fischer's exact test

Figure 1. Immunohistochemical CD10 expression in malignant melanoma (MM)
a. Representative pleomorphic MM. **b.** Diffuse 3+ CD10 expression in MM cells. **c.** CD10 expression, 2+, seen in less than 50% of MM cells. **d.** A few CD10⁺ tumor cells, 1+. **e.** MM with intratumoral or intercellular stromal cells. **f.** Intratumoral proliferation of CD10⁺ stromal cells. **g.** MM with peritumoral proliferation of fibrous stromal tissue (fibroblast). **h.** Peritumoral expression of CD10⁺ stromal cells. Magnification: 200× for **a-h**; 400× for inset of **a-d**.

though benign and malignant melanocytic lesions essentially differ, those with wide dermal involvement can be difficult to distinguish morphologically. Use of IHC to diagnose melanocytic lesions³⁻⁵) also did not completely present a clear way to discriminate

between these lesions.

CD10, also known as neutral endopeptidase, enkephalinase, neprilisin, or common acute lymphoblastic leukemia antigen (CALLA), is a zinc-dependent metalloproteinase located on the cell surface¹⁴⁾ and is

Figure 2. Nevus with CD10⁺ stromal cells. **a.** Pigmented nevus in deep dermis. **b.** CD10⁺ fine stromal cells near vessels in the deep dermis. **c.** Nevus cells around hair follicles (F) and vessels (V). **d.** CD10⁺ stromal cells extended from around the hair follicles and vessels. **e.** Nevus with granulocytic infiltration. **f.** Fine CD10⁺ stromal cells between nevus cells, associated with infiltrating CD10⁺ granulocytes. Magnification: 200× for **a**, **b**, **e**, **f**; 100× for **c**, **d**.

Table 3. Sensitivity, Specificity, PPV, and NPV for CD10 Expression in Melanocytic Lesions

	Tumoral cells (%)		Tumoral and/or stromal cells (%)	
	MM	Nevus	MM	Nevus
Sensitivity	47	0	94	16
Specificity	100	53	84	6
PPV	100	0	81	19
NPV	73	28	96	5

PPV: positive predictive value; NPV: negative predictive value.

expressed in many normal cells, including myoepithelial breast cells²³, proximal uriniferous tubules²⁴, stromal endometrial cells²⁵, and stromal cells of skin appendages¹⁸, as well as many benign or malignant tumors¹¹⁾¹³. Chu et al.¹¹ found CD10 expressed in renal cell carcinoma, transitional cell carcinoma, prostatic adenocarcinoma, endometrial stromal sarcoma, rhabdomyosarcoma, and schwannoma. Hematopathological malignancies, including acute lymphoblastic leukemia, follicular lymphoma, Burkitt lymphoma, and angioimmunoblastic T-cell lymphoma, also express CD10¹⁰⁾²⁶, with diffuse cytoplasmic and/or membranous IHC staining patterns. For MM, Carrel et al.¹⁶⁾¹⁷ showed CD10 expression in 63% and 38% of ocular and cutaneous tumor tissues, respectively. Kianitakis et al.⁶ found that frequency of CD10 expression in MMs was higher in metastatic lesions in skin (69.0%) or lymph nodes (61.0%) than in primary tumors (21.4%), in accordance with several other reports⁷⁻⁹. These results suggest a close relationship between up-regulation of CD10 and tumor progression in MM. However, CD10 expression in BMN, a benign counterpart to MM, has not been fully explained²⁰. To evaluate the usefulness of CD10 IHC to distinguish malignant and benign melanocytic lesions, we studied CD10 expression patterns in primary cutaneous MMs and BMN.

In primary cutaneous MMs, tumor cell expression ranged from 3.0 – 53.8% in previous reports⁷⁻⁹⁾²⁰⁾²⁷. In this study, CD10⁺ tumor cells were seen in 17 of 36 cases (47.2%), for which this assay was 47% sensitive and 100% specific, with 100% PPV and 73% NPV. As this method was not highly sensitive for the diagnosis of MMs, CD10 should not be a representative tumor marker in MM. However, as no BMN cells produced CD10 antigen, this test was 100% specific and had a 100% PPV in this study, which suggests that CD10 could be a useful marker for malignancy.

CD10 expression has not been widely studied in BMN. Oba et al.²⁰ reported a CD10 expression study relating to tumor progression and prognosis of MMs compared with melanocytic nevi. They reported 34 of 64 (53%) primary MM specimens and 4 of 40 (10%) BMN specimens expressed CD10, similar to our results in the present study, although four melanocytic nevi (2 Spitz and 2 compound nevi) were CD10⁺. The CD10⁻ specimens in this investigation were 14 compound, 14 junctional, 4 Spitz, and 4 dysplastic nevi; Spitz nevi were suggested to be more likely to express CD10 compared with common or dysplastic

nevi. Spitz and dysplastic nevi are special BMN types that could be difficult to distinguish from melanoma, and warrant further study. Although Oba et al.²⁰ found common BMN could express CD10, we found no CD10⁺ BMN tumoral cells in the present study. Additional BMN specimens are needed to clarify the expression of CD10 in common melanocytic nevi, as well as Spitz and dysplastic nevi.

Stromal proliferation is not unusual in invasive malignant neoplasms. Proliferation of CD10⁺ stromal cells has been reported in other organs. Stromal expression of CD10 in invasive breast carcinoma is reportedly associated with increasing tumor grade and worsening prognosis²⁸⁻³⁰. Ogawa et al.³¹ showed that CD10⁺ stromal cells in colorectal carcinoma were associated with tumor progression. As CD10⁺ stromal cells are frequently seen near or at the invasive fronts of tumors, CD10 may be involved in the interaction between neoplastic cells and stromal cells²⁸⁻³¹. In this study, two types of CD10⁺ stromal cell reactions were found in MMs, namely intratumoral proliferation pattern (**Fig. 1e, f**) and peritumoral proliferation pattern (**Fig. 1g, h**). Bialovic et al.⁷ first described these two types of stromal cells and associated CD10⁺ stromal cells with tumor progression. In MMs, neoplastic cells and CD10⁺ stromal cells appear to have some relationship. Among the 50 nevus samples, 8 (16.0%) had CD10⁺ stromal cells, of which 7 showed only a focal and fine positivity with the positive cells located in the perivascular areas of deep dermis (**Fig. 2a-d**). The eighth specimen showed relatively diffuse positivity in the lesion and was associated with a dermal ulcer with diffuse infiltration of inflammatory cells. In some of our MM specimens, CD10⁺ stromal cells tended to proliferate around vessels near skin ulcers, suggesting that CD10⁺ stromal cells around vessels and skin appendages may increase under the influence of inflammation. The function of CD10⁺ stromal cells in tumors has not been widely studied. Xie et al.³² reported that the CD10⁺ fibroblasts inhibited the invasive capacity of interleukin-1 α -producing squamous cell carcinoma by diminishing substance P. As infiltration of peritumoral CD10⁺ stromal cells in squamous cell carcinoma is similar to that seen in CD10⁺ stromal cells in MM, they could share similar functions as inhibitors of tumor invasion. At least two patterns of CD10⁺ stromal cell infiltration were seen, indicating the possibility of several mechanisms and relationships with MM development. Maguer-Satta et al.¹⁴ suggested that CD10 is supported by two major mechanisms: 1) extracellular enzymatic activity on

surfaces of epithelial and stromal cells; and 2) intracellular signaling that interferes with other major signaling pathways. These CD10 mechanisms regulate biological functions of normal and malignant stem cells and their environments.

We found 34 CD10⁺ samples out of 36 MM cases (94.4%) in both or either tumor and stromal cells, compared with 8 out of 50 BMN samples (16.0%) in stromal cells only. This method was 94% sensitive and 84% specific, with an 81% PPV and a 96% NPV. The IHC sensitivity for tumoral and/or stromal expression of CD10 is higher than that for tumoral expression only, indicating that combining tumoral and stromal CD10 expression would be the best approach for its use in diagnosis of MM.

In conclusion, this study suggests a potential utility of CD10 in differentiating advanced MM from benign melanocytic lesion. IHC CD10 expression in either tumor or stromal cells could indicate higher possibilities of malignant disease. However, CD10 staining that is negative or fine and focally positive may represent benign lesions. Although clinical and pathological evaluation is essential for making final diagnoses, immunohistochemical CD10 expression could help distinguish MM and BMN.

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