Expression of cell cycle inhibitor p27^{Kip1} in nevi and melanomas

Sir,

Cutaneous melanoma, the most aggressive skin tumor, is characterized by a multifactorial etiology.[1] Multiple genetic alterations including oncogens, tumor suppressor genes, and apoptosis-related genes can cause conversion of normal cells to cancer cells.[2] It has been suggested that proliferation and progression of cancer cells relate to abnormalities in various cell cycle regulators. Cell cycle is controlled by the regulators such as cyclins, cyclin-dependent kinases, and their inhibitors. P27^{Kip1} is an important cyclin-dependent kinase inhibitor. It has crucial roles in cellular processes, which cause G1 arrest when overexpressed; and it functions as a tumor suppressor.[3]

There are conflicted data of p27^{Kip1} expression in melanoma and dysplastic nevi. Besides low levels of p27^{Kip1}, normal levels have also been reported to be associated with melanoma.[3] The aim of the present study was to investigate the expression of p27^{Kip1} in melanocyctic lesions, and to identify its possible participation in melanoma progression.

Paraffin-embedded archival tissues from 45 patients with benign nevi (14), dysplastic nevi (15), and melanoma (16) diagnosed between 1991 and 2007 were evaluated for expression of p27^{Kip1} by immunohistochemistry. Medical records were reviewed for each case for demographic data, as well as clinical and pathologic characteristics. All the samples were evaluated by the same pathologist, and strong nuclear staining was accepted as positive. In every sample, 10 fields were taken and 500 cells were evaluated for each field (40x). For every field, mean values were calculated for positive nuclear stained cells. Differences of P27^{Kip1} expression between groups were evaluated by nonparametric test (Mann-Whitney U test). A value of $P < 0.05$ was considered significant.

Sixteen unrelated patients (6 women, 10 men; mean±SD age, 55.56±16.35 years) with melanoma; 15 patients (8 women, 7 men; mean±SD age, 36.73±7.71 years) with dysplastic nevi; and 14 patients (7 women, 7 men; mean±SD age, 28.71±6.79 years) with benign nevi were enrolled in the study. Expression of p27^{Kip1} as the number of positive nuclei was 454.46±26.6 (91%) for the benign nevi, 452±21.7 (90.6%) for the dysplastic nevi, and 313±42.8 (62.6%) for the melanomas [Figures 1A, B]. A significant difference was observed in expression of p27^{Kip1} between benign nevi and melanomas ($P < 0.001$). There was also a significant difference in expression of p27^{Kip1} between dysplastic nevi

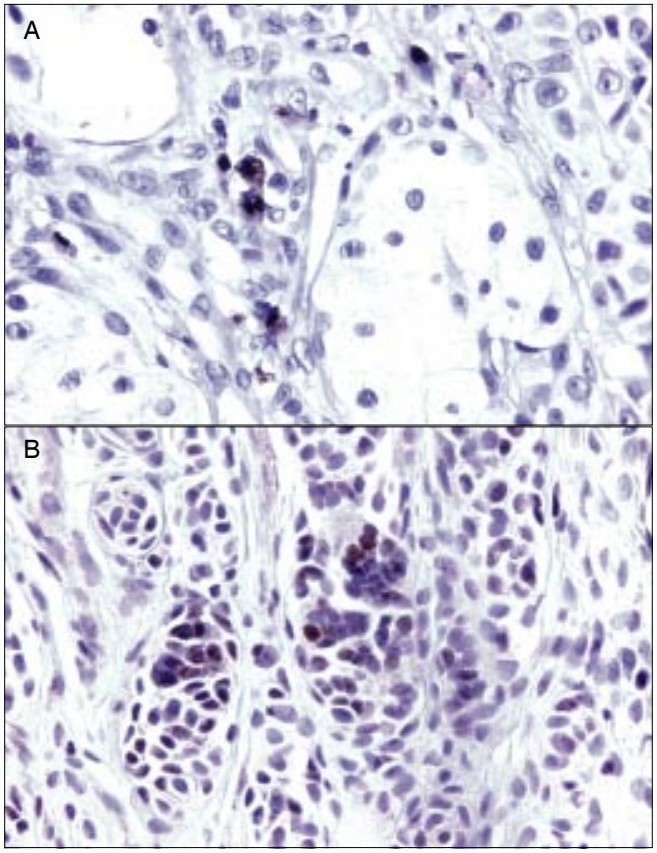

Figure 1: (A) P27 immunostaining: balloon cell melanoma (×400). (B) Intradermal nevus (×400)

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Table 1: Immunohistochemical staining results of benign nevi, dysplastic nevi, and melanoma

	Dysplastic nevi (n=15)	Melanoma (n=16)	Benign nevi (n=14)	*P*
p27^{Kip1} (%)	452,47±21,86 (90.6)	313,06±42,83 (62.6)	454,46±21,86 (91)	*P*<0.001

Table 2: Immunohistochemical staining results of melanomacases according to the clinical and pathological features

Melanoma (n=16)	p27^{Kip1} (%)	*P*
Metastase + (n=8)	302,75±40,90 (60.6)	0.40
Metastase - (n=8)	323,38±44,90 (64.6)	
Ulceration + (n=7)	296,00±43,80 (59.2)	0.07
Ulceration - (n=9)	330,13±36,71 (66)	
Clark level IV-V (n=8)	307,38±50,64 (61.4)	0.44
Clark level I-III (n=8)	318,75±35,96 (63.8)	
Breslow > 4 mm (n=6)	307,50±40,99 (61.6)	0.74
Breslow < 4 mm (n=10)	322,33±48,09 (64.4)	
Male (n=10)	308,6±45,9 (61.8)	0.50
Female (n=6)	320,5±40,1 (64.2)	

and melanomas ($P < 0.001$) [Table 1]. In melanoma cases, when the p27^{Kip1} expression was analyzed according to the clinical and pathological features, it was seen that the expression was decreased in patients with metastasis, ulceration, increased tumor thickness, and male sex. But none of these changes were statistically significantly [Table 2].

In the present study we found that p27^{Kip1} expression was significantly lower in melanoma patients compared to patients with benign nevi and dysplastic nevi. Morgan *et al,* analyzed p27^{Kip1} expression in 63 melanocyctic lesions (21 Spitz nevi, 21 compound nevi, and 21 melanomas).[4] They did not report any difference in p27^{Kip1} staining. On the other hand, Ivan *et al,* also examined p27^{Kip1} protein levels in melanocytic lesions (15 nevi, 18 dysplastic nevi, and 15 melanomas), and they reported lower expression levels of p27^{Kip1} in melanoma cases. In agreement with this report for benign and dysplastic nevi, we found that p27^{Kip1} was highly expressed in these lesions, supporting the notion that one important function of p27^{Kip1} may be to regulate stillness in nevi cells. The level of p27^{Kip1} has been shown to be regulated primarily at the post-transcriptional level through the ubiquitin-proteasome-mediated pathway.[5] The low level of p27^{Kip1} in cancers is suggested to be due to an enhancement of its degradation and decreased stability.[3] A potential role of the extracellular matrix has also been proposed for inducing p27^{Kip1} degradation in melanoma.[6]

Melanoma cell proliferation is an important parameter in determining the biological behavior of melanoma. p27^{Kip1} has been suggested to have functions related to cell adhesion and may play a role in tumor invasion and metastasis by allowing cells to escape from the primary site. Florenes *et al,* have shown lower p27^{Kip1} expression in thicker lesions in cases with nodular melanomas. In addition, they found that patients having tumors with fewer than 5% p27^{Kip1} staining cells had a significantly higher risk of early relapse of their disease compared with those expressing moderate or high levels.[7]

Our results suggest that p27^{Kip1} could play a critical role in the genesis and progression of melanoma, and future studies will be required to determine therapeutic importance of p27^{Kip1}, in addition to the prognostic value.

Ayse Akman, M. Akif Ciftcioglu[1], Caner Ozbey[1], Erkan Alpsoy

Departments of Dermatology and Venereology, and [1]Pathology, Akdeniz University School of Medicine, Antalya, Turkey

Address for correspondence: Dr. Ayse Akman, Department of Dermatology and Venereology, Akdeniz University School of Medicine, 07070 Antalya, Turkey E-mail: aakman@akdeniz.edu.tr

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