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Jorge S. Reis-Filho · Beatriz Torio
André Albergaria · Fernando C. Schmitt

Maspin expression in normal skin and usual cutaneous carcinomas

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Abstract Maspin is a serine protease inhibitor whose gene is located on 3q27. Several lines of evidence point towards its putative role as tumor suppressor gene and angiogenesis inhibitor; however, there are compelling data showing that maspin is also expressed in the nuclear compartment and might be associated with the differentiation of specific cell lineages. No systematic study of maspin expression in normal skin and usual skin carcinomas have been published so far. We semiquantitatively analyzed the distribution and immunoreactivity pattern of maspin in 14 squamous cell carcinomas (SCCs) and 16 basal cell carcinomas (BCCs) and in the adjacent normal epidermis of all cases. We also examined the correlation of maspin expression with histological type, grade, vascular invasion, perineural infiltration, and mitotic counting. Cytoplasmic expression of maspin was observed in suprabasal, prickle, and granular cell layers of normal epidermis; cells of the germinative hair matrix, Henle's and Huxley's layers, and cuticle of hair follicles; mature sebaceous cells and sweat gland's secretory cells. Nuclear expression was detected in some basal/myoepithelial cells of the sweat glands and scattered mature sebaceous cells. All SCCs but one grade IV SCC showed maspin expression, and it was correlated with the differentiation of these neoplasms. BCCs presented variable maspin expression, while metatypical carcinomas showed moderate to intense maspin expression, nodular BCCs variable contents of maspin and displayed a peculiar distribution, confined to the center of the neoplastic nodules. Two BCCs and one SCC showed maspin nuclear expression. No correlation with other clinical pathological features was observed. Our findings do not support the role of maspin as a tumor suppressor gene and suggest that this serpin is probably associated with specific lines of differentiation.

Keywords Maspin · Squamous cell carcinoma · Basal cell carcinoma · Immunohistochemistry

J.S. Reis-Filho (✉)
R. Roberto Frias S/N, 4200 Porto Portugal
e-mail: jreis@ipatimup.pt
Tel.: +351-2-25570700
Fax: +351-2-25570799

J.S. Reis-Filho · F.C. Schmitt
Institute of Molecular Biology and Immunology,
University of Porto, Porto, Portugal

J.S. Reis-Filho
School of Health Sciences, University of Minho,
Braga, Portugal

B. Torio
Department of Pathology, Hospital Fernando da Fonseca,
Amadora-Sintra, Lisbon, Portugal

A. Albergaria
Institute of Molecular Biology and Immunology,
University of Porto, Porto, Portugal

F.C. Schmitt
Department of Pathology, Porto Medical Faculty,
University of Porto, Porto, Portugal

Introduction

Mammary serpin, also known as maspin, is a serine protease inhibitor that was originally isolated by subtractive hybridization and differential display techniques comparing mammary epithelial cells and mammary carcinomas [9, 14, 37]. Its gene is located on 18q21 and encodes a serine protease inhibitor of 42 kDa that putatively has tumor suppressor [9, 14, 15, 22, 27, 28, 37] and antiangiogenic activity [9, 14, 36, 37]. Moreover it has been proposed that maspin blocks plasminogen activator [27, 28], a factor that mediates cellular invasion and migration. Despite the huge amount of data concerning the expression of maspin and its correlations with biological properties of human breast [9, 14, 15, 22, 27, 28, 36, 37], prostate [18, 27, 31, 35], and pancreatic carcinomas [16, 17] and cell lines [9, 14, 15, 16, 17, 18, 22, 27, 28, 31, 35, 36, 37], little is know on maspin expression in other tissues.

Recently our group [23, 25] and others [12, 17, 20] demonstrated that maspin is consistently expressed in normal and hyperplastic myoepithelial cells and in myoepithelial cell tumors. Moreover, we also observed that peculiarly aggressive types of breast neoplasms do express maspin [24] despite their very aggressive behavior.

In addition, it has been reported that maspin is also expressed in the nuclei of myoepithelial [23, 25], pancreatic [17], and breast secretory cells [20]. These findings prompted us to evaluate the hypothesis that maspin expression is also associated with specific differentiations in some cell types.

Myoepithelial cells and terminally differentiated squamous cells show some similarities regarding differentiation markers, such as keratins 5 and 14. In addition, Katz and Taichman [11], using two-dimensional gel electrophoresis, have reported that maspin is one of the serpins secreted by human keratinocytes. We therefore hypothesized that maspin is expressed in keratinocytes and in epidermal tumors. Interestingly, no systematic evaluation of maspin expression in normal cutaneous tissues or usual skin carcinomas has yet been performed. We describe here the expression of maspin in normal epidermis, cutaneous appendages, in situ squamous cell carcinoma (SCC), invasive SCC, and basal cell carcinoma (BCC).

Material and methods

Cases selection

Fourteen consecutive cases of SCC, with and without an associate in situ component, and 17 consecutive cases of BCC were retrospectively retrieved from the files of the Department of Pathology, Hospital Fernando da Fonseca, Lisbon, Portugal. Patients' ages ranged from 32 to 82 years (median: SCCs 62, BCCs 73.5). All patients were white and all tumors affected sun-exposed skin. Table 1 summarizes the clinical pathological data. The clinical and pathological data were collected from the pathology reports. All cases were independently reviewed by three of the authors (J.S.R.F., B.T., F.C.S.) and the diagnoses were reconfirmed in all but one case (one "metatypical" carcinoma was reclassified as SCC). SCCs were graded according to Broders' criteria [13, 19] and BCCs were classified according to Rippey's classification [26]. All cases were also classified according to the presence of in situ component, growth pattern (infiltrative vs. expansive), degree of desmoplasia, presence of vascular/lymphatic invasion, and perineurial infiltration. Mitotic counting was performed by two of the authors (J.S.R.F., B.T.) and is reported as the number of mitotic figures per ten consecutive high power magnification fields (HPF) in the most proliferative areas.

Immunohistochemical analysis

For all cases a 4-μm histological section was cut and mounted on a silane-coated slide. Immunohistochemistry using the streptavidin-biotin-peroxidase technique with a monoclonal antibody raised against maspin (Novocastra, clone EAW24, 1:50, Newcastle, UK) was performed as described elsewhere [23]. Heat-induced antigen retrieval using Dako Antigen Retrieval Solution (Dako, Glostrup, Denmark) was previously performed in a wet bath during 20 min in all cases. Positive and negative controls were included in each slide run. Nuclear, cytoplasmic, and membranous staining were accepted as specific.

The distribution of maspin expression was evaluated in normal epidermis, sweat glands, sebaceous glands, hair follicles, dermal

Table 1 Summary of pathological clinical data of the cases (*BCC* basal cell carcinoma, *ND* not done, *SCC* squamous cell carcinoma)

Biopsy no.	Age (years)	Diagnosis	Histological type/grade	Borders	Desmoplasia	Perineurial invasion	Vascular invasion	Mitotic counting
1	77	BCC	Metatypical	Infiltrative	Intense	Present	Absent	24
2	66	BCC	Metatypical	Infiltrative	Intense	Absent	Absent	34
3	75	BCC	Metatypical	Infiltrative	Intense	Absent	Present	56
4	82	BCC	Nodular	Expansive	Low	Absent	Absent	18
5	80	BCC	Mixed	Infiltrative	Low	Absent	Absent	29
6	59	BCC	Mixed	Infiltrative	Moderate	Absent	Absent	23
7	62	BCC	Mixed	Infiltrative	Moderate	Absent	Present	31
8	72	BCC	Nodular	Expansive	Low	Absent	Absent	42
9	70	BCC	Nodular	Expansive	Moderate	Absent	Absent	10
10	75	BCC	Nodular	Expansive	Low	Absent	Absent	19
11	80	BCC	Micronodular	Expansive	Low	Absent	Absent	4
12	63	BCC	Nodular	Expansive	Low	Absent	Absent	2
13	75	BCC	Nodular	Expansive	Low	Absent	Absent	46
14	64	BCC	Nodular	Expansive	Low	Absent	Absent	16
15	64	BCC	Nodular	Expansive	Low	Absent	Absent	8
16	75	BCC	Nodular	Expansive	Low	Absent	Absent	ND[a]
17	76	SCC	Grade I	Expansive	Moderate	Absent	Absent	11
18	75	SCC	Grade I	Expansive	Moderate	Absent	Absent	26
19	67	SCC	Grade I	Infiltrative	Moderate	Absent	Absent	30
20	54	SCC	Grade I	Infiltrative	Intense	Absent	Absent	45
21	57	SCC	Grade II	Infiltrative	Moderate	Absent	Present	54
22	66	SCC	Grade II	Infiltrative	Moderate	Present	Present	13
23	42	SCC	Grade II	Infiltrative	Moderate	Present	Absent	26
24	32	SCC	Grade II	Infiltrative	Intense	Absent	Absent	33
25	74	SCC	Grade II	Infiltrative	Moderate	Absent	Absent	13
26	55	SCC	Grade III	Expansive	Moderate	Absent	Absent	33
27	71	SCC	Grade III	Infiltrative	Moderate	Absent	Absent	19
28	59	SCC	Grade III	Infiltrative	Moderate	Absent	Present	181
29	62	SCC	Grade III	Infiltrative	Moderate	Absent	Present	74
30	67	SCC	Grade IV, spindle cell carcinoma	Infiltrative	Moderate	Present	Present	16

[a] Insufficient tumor area to proceed mitotic counting

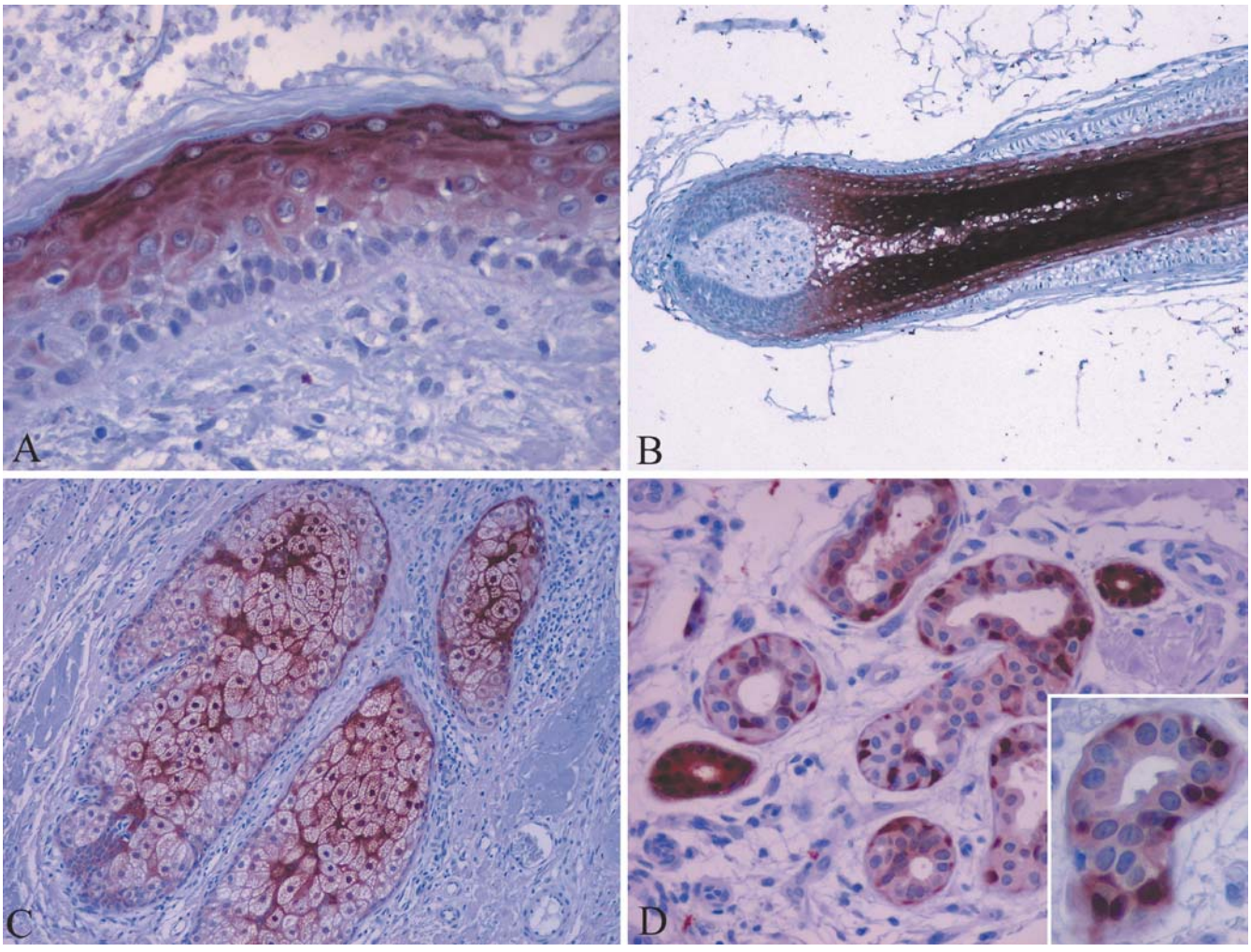

Fig. 1A–D Maspin expression in normal skin. **A** Normal epidermis showing maspin expression in suprabasal, and granulous prickle layers. **B** Hair follicle, anagen growth phase: maspin expression in mature hair matrix cells and cells of the Henley's and Huxley's layers and in the hair cuticle. **C** Sebaceous glands decorated by maspin. **D** Sweat glands showing maspin nuclear expression in basal cells and some secretory cells with cytoplasmic and nuclear expression. *Inset* Note nuclear expression in basal cells of an eccrine sweat gland. Streptavidin-biotin-peroxidase/DAB, original magnification: **A** ×400; B, C ×100X; **D** ×200

mesenchymal cells, endothelial cells, pericytes, erector muscles, nerve bundles, and adipocytes. Semiquantitative assessment of maspin expression was performed for in situ SCCs, invasive SCCs, and BCCs, according to the following criteria: - negative nuclear staining of neoplastic cells; +, focal (<5%) positivity of neoplastic cells; ++, moderate (5–50%) positivity of neoplastic cells; +++, diffuse (>50%) positivity of neoplastic cells. Owing to the remarkable differential expression of maspin in cells showing basal cell-like/undifferentiated morphology and terminally differentiation morphology in SCC and BCC, maspin expression was semiquantified separately in each cell type. Moreover, we also evaluated the overall nuclear and cytoplasmic maspin expression in both cell types.

Statistical analysis

Statistical analysis was evaluated using Statview software. Statistical differences between maspin expression and histological type, histological grade of SCCs, BCC types, presence of vascular/lymphatic invasion, presence of perineurial infiltration were calculated using χ^2 test. Analysis of variance with Yates' correction was used to compare the extension and pattern of maspin expression mean values for mitotic counting. Differences at the level of $P<0.05$ were considered statistically significant.

Results

Clinical and pathological data

All SCCs showed variable keratinization; according to Broders' criteria [13, 19], four were classified as grade I, five as grade II, four as grade III, and one as grade IV. The grade IV was a bona fide example of spindle cell SCC, showing intersecting fascicles of variably pleomorphic spindle cells. In seven cases an associated in situ component was depicted [13, 19]. Eleven cases showed infiltrative borders and three a remarkably expansive growth pattern. Twelve cases showed moderate desmoplasia and two intense desmoplastic stroma. Vascular/lymphatic invasion was observed in five cases, and perineurial invasion in only three cases. Mitotic figures ranged from 11 to 181 per 10 HPF, with a mean of 41 in SCCs and 28 in BCCs.

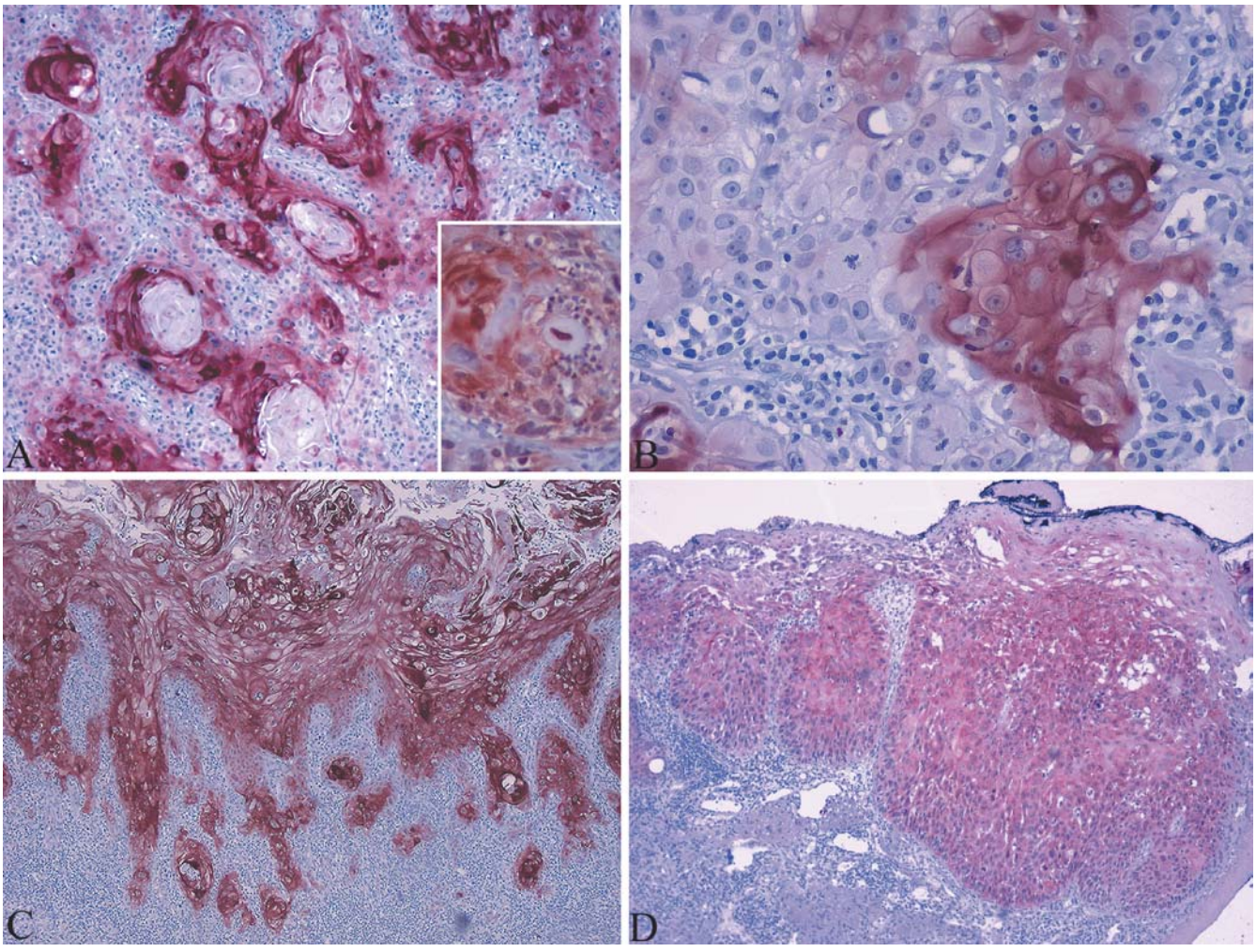

Fig. 2A–D Maspin expression in squamous cell carcinomas (SCCs). **A** SCC, grade II. Maspin expression in the cytoplasm of mature squamous cells. *Inset* Note a mature squamous cell with maspin nuclear expression in the center of a squamous pearl. **B** Scattered maspin expression in grade III SCC. **C** SCC, grade I. Maspin strongly decorated neoplastic cells in a cytoplasmic and membranous pattern. **D** SCC in situ adjacent to invasive grade III. Note reduction in maspin expression in the suprabasal layers of the skin. Streptavidin-biotin-peroxidase/DAB, original magnification: **A** ×100; **A** *inset*, **B** ×400; **C** ×40; **D** ×100

Concerning BCCs, the histological subtypes [26] are described in Table 1. Ten cases were of the nodular histological type (including four with an adenoid pattern) and three of the mixed type. In three cases there was a complex admixture of two types of cells: (a) cells with darkly stained nuclei and scant cytoplasm, indistinguishable from those observed in bona fide BCCs; (b) neoplastic cells showing a more vesicular and atypical nuclei, with prominent nucleoli, and more abundant eosinophilic cytoplasm. In all of these cases the neoplastic cells were arranged in infiltrative cords with ill-defined peripheral palisades immersed in a highly desmoplastic stroma, showing obvious stromal-epithelial separation artifacts; moreover, features of squamous differentiation were observed unevenly, but squamous pearls were not found [1]. We preferred to classify these cases as metatypical carcinomas, but obviously these cases could also be classified as BCC with incomplete squamous differentiation, infiltrative borders, and intense desmoplasia [1, 19]. Ten cases had expansive borders and six infiltrative growth pattern. Ten cases showed low desmoplastic stromal reaction; moderate and intense desmoplasia was observed in three cases each. There was vascular/lymphatic invasion in one case and perineurial infiltration in two others. Mitotic figures ranged from 2 to 56 per 10 HPF, with a mean of 24.1 in SCCs and 23.0 in BCCs.

Maspin expression

Normal skin

In normal epidermis there was a gradual increase in cytoplasmic and membranous expression of maspin from the suprabasal to spinous and granular layers (Fig. 1A). Basal cells were uniformly negative. It should be noted that all keratinized cutaneous structures showed maspin expression. In hair follicles maspin was consistently expressed in the cytoplasms and on the membranes of mature cells of germinative hair matrix layer; a cytoplasmic and mem-

Table 2 Maspin expression in usual cutaneous carcinomas [– negative staining, + focal positivity (<5% of neoplastic cells), ++ moderate positivity (5–50% of neoplastic cells), +++ diffuse immunoreactivity (>50% of neoplastic cells), *BCC* basal cell carcinoma, *SCC* squamous cell carcinoma]

Case no.	Diagnosis	Histological type/grade	Maspin cell type		Maspin overall immunoreactivity	
			Squamous cells	Undifferentiated basal cells	Nucleus	Cytoplasm, membrane
1	BCC	Metatypical	+++	+	+	++
2	BCC	Metatypical	++	++	–	+++
3	BCC	Metatypical	++	++	–	+++
4	BCC	Nodular	+++	++	++	+++
5	BCC	Mixed	–	–	–	–
6	BCC	Mixed	+	+	–	++
7	BCC	Mixed	+++	+++	–	+++
8	BCC	Nodular	–	++	–	+
9	BCC	Nodular	–	–	–	–
10	BCC	Nodular	–	++	–	+++
11	BCC	Micronodular	–	+	+	+
12	BCC	Nodular	–	–	–	–
13	BCC	Nodular	–	++	–	++
14	BCC	Nodular	+	++	–	++
15	BCC	Nodular	+	+	–	+
16	BCC	Nodular	–	–	–	–
17	SCC	Grade I	+++	+	–	+++
18	SCC	Grade I	+++	–	–	+++
19	SCC	Grade I	+++	++	–	+++
20	SCC	Grade I	+++	–	–	+++
21	SCC	Grade II	+++	++	+	+++
22	SCC	Grade II	+++	+	–	+++
23	SCC	Grade II	+++	+	–	+++
24	SCC	Grade II	++	–	–	++
25	SCC	Grade II	+	–	–	+
26	SCC	Grade III	+	–	–	–
27	SCC	Grade III	+	–	–	+
28	SCC	Grade III	+++	–	–	+++
29	SCC	Grade III	+++	–	–	+
30	SCC	Grade IV, spindle cell carcinoma	–	–	–	–

branous reactivity was also observed in the Henle's and Huxley's layers as well as in the hair cuticle; focal expression of maspin was also observed in some of the cells of the external root sheath of the hair follicles (Fig. 1B). No immunoreactivity was observed the perifollicular connective tissue sheath. Mature sebaceous cells showed intense cytoplasmic reactivity for maspin as well as occasional nuclear immunoreactivity (Fig. 1C). By contrast, sweat glands showed a remarkably uneven distribution of maspin staining. While some glands showed nuclear and cytoplasmic immunoreactivity in all cells, others showed only nuclear positivity in cells arranged in a basal cell or myoepithelial-like pattern (Fig. 1D), in a similar pattern to what has been described for maspin expression in breast lobules and ducts. No dermal mesenchymal cell, endothelial cell, pericyte, smooth muscle cell, neural cell, or adipocyte showed any immunoreactivity for maspin.

Squamous cell carcinomas

The cell type specific and overall expression of maspin is summarized in Table 2. The overall cytoplasmic expression of maspin in SCCs was largely dependent on the proportion of keratinized cells and on the tumors' grade (Fig. 2A). Squamous pearls showed intense cytoplasmic/membranous maspin immunoreactivity in the cells around the keratinized foci (Fig. 2B). Conversely, undifferentiated cells lacked maspin immunoreactivity or only showed focal and weak staining. Focal nuclear maspin positivity was only observed in one grade II SCC (Fig. 2A, inset).

In relation to grade, overall cytoplasmic maspin staining was more diffuse in well differentiated (grade I and grade II) SCCs than poorly differentiated (grade III and grade IV) SCCs (P=0.0099). Briefly, all grade I tumors showed +++ positivity (Fig. 2C), four grade II tumors were diffusely (+++) positive for maspin, one case showed moderate and other focal immunoreactivity; in grade III tumors, maspin was absent in one case, focally expressed in two, and diffusely expressed in one. The grade IV spindle cell carcinoma was completely negative for this marker. The degree of desmoplasia showed a trend to be inversely correlated with maspin cytoplasmic expression (P=0.0767). Maspin did not show any other statistical correlation with other pathological parameters.

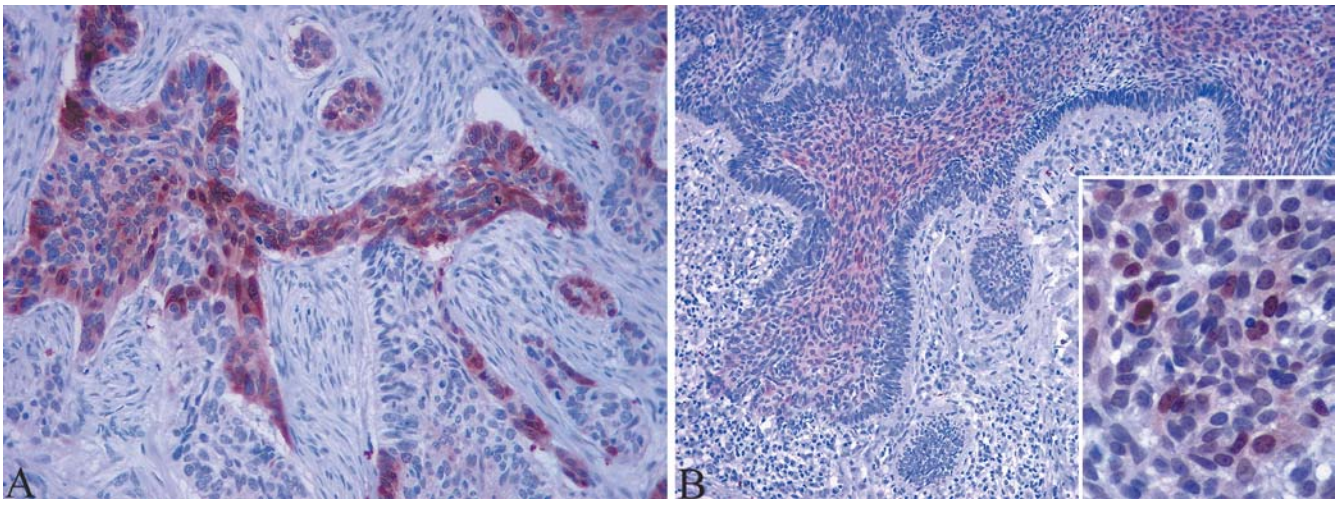

Fig. 3A–D Maspin expression in basal cell carcinomas. **A** BCC with invasive borders and intense desmoplasia: maspin is expressed at the periphery and center of infiltrative cords. **B** BCC, nodular type: maspin is expressed in the center of the nodules. Note that peripheral palisading basal cells lack maspin expression. *Inset* Maspin expression in the nuclei of scattered neoplastic basal cells. Streptavidin-biotin-peroxidase/DAB, original magnification: **A** ×200; **B** ×100; **B** *inset* ×400X

A marked reduction in maspin expression was observed in four of seven in situ SCCs when compared to adjacent epidermis; while in normal and reactive epidermis maspin was consistently expressed in the superficial layers, in in situ SCCs it was markedly reduced and confined either to the suprabasal or suprabasal and spinous layers (Fig. 2D). However, it should be noted that the cases evaluated here were associated with invasive SCCs and may not reflect the distribution of maspin in preneoplastic lesions of the skin.

Basal cell carcinomas

All "metatypical" BCCs showed moderate to diffuse overall cytoplasmic expression of maspin. Three nodular BCCs lacked maspin immunoreactivity; two were focally (+) positive; two were moderately immunoreactive (++); and three showed immunoreactivity in more than 50% of neoplastic cells (+++). Mixed BCCs showed highly variable overall maspin expression; one case was negative, one focally positive, and one diffusely immunoreactive. Notably, nodular and mixed BCCs showed an interesting pattern of maspin immunoreactivity, with maspin positive cells confined to the central region of the neoplastic clusters (Fig. 3A). However, in metatypical BCCs maspin was expressed either in the central as in the periphery of cells cords and clusters (Fig. 3B). There was no statistical correlation between overall maspin expression and other pathological parameters. Concerning nuclear expression of maspin, only two nodular BCCs and one metatypical BCC revealed this pattern of reactivity.

Discussion

Maspin is one of the serpins that have received great attention by basic researchers and pathologists during the past few years [9, 5, 6, 11, 12, 14, 15, 16, 17, 18, 20, 21, 22, 23, 24, 25, 27, 28, 31, 35, 36, 37]. Since its characterization several biological properties have been attributed to maspin, including tumor suppressor and antiangiogenic activities [9, 14, 15, 22, 27, 28, 36, 37]. It is also considered as a suppressor of invasion, motility, proliferation, and metastatic potential of neoplastic cells [9, 5, 6, 11, 12, 14, 15, 16, 17, 18, 20, 21, 22, 23, 24, 25, 27, 28, 31, 35, 36, 37]. Moreover, there are controversial data on the role of maspin as a downstream factor of p53 pathway [9, 14, 18, 33, 37, 38].

Much has been reported regarding maspin function and its subcellular localization [9, 17, 20, 21, 23, 27]. Some studies describe maspin as a soluble cytoplasmic protein that associates with secretory vesicles and is also present on the cell surface [21, 27]. We [23, 24, 25] and others [12, 17, 20] have demonstrated that maspin is also expressed in the nuclei of myoepihelial cells, myoepithelial cell tumors, and in some breast carcinomas [12, 20, 23, 24, 25]. However, in the present study we report for the first time, maspin expression in the nuclei of scattered neoplastic cells in SCCs and BCCs. Moreover, sweat gland basal cells were consistently decorated by maspin, both in nuclear and cytoplasmic compartments. These observations are in accordance with the findings of Takeda et al. [30], who analyzed the expression SCC antigens 1 and 2 in psoriatic skin samples using conventional immunohistochemistry and immunoelectron microscopy and found that these serpins are abundantly expressed in the nuclei of the granular layer cells and of keratinocytes of elongated rete ridges [37]. Moreover, ovalbumin, another serpin, may also present a nucleocytoplasmic distribution [4].

Similar findings regarding myeloid and erythroid nuclear termination stage-specific protein nuclear expression have been published by Irving et al. [10]. In the nuclear compartment this serpin plays a very interesting

role in chromatin structure and in cell proliferation [10]. Based on these findings [4, 10, 12, 17, 20, 23, 24, 25, 37] one might hypothesize that nuclear expression of maspin is related to specific histogenetic phenotypes and/or pathways of differentiation, and that some of the tumor suppressing properties previously reported for maspin are related to its putative functions on chromatin remodeling and cell proliferation. Obviously further studies are needed to clarify the intriguing roles of maspin in the nuclei of normal and neoplastic cells.

Recently, Xia et al. [33] and Yasumatsu et al. [34] demonstrated that maspin is expressed in a subset of oral SCCs with favorable prognosis; in accordance with the findings of Yasumatsu et al. [34], in the present study we also observed that maspin is preferentially expressed in well-differentiated SCCs. Moreover, maspin was consistently expressed in almost all squamous pearls. As previously reported [33, 34], maspin expression was not statistically correlated with other pathological features of SCCs, including cell proliferation, growth pattern, and degree of desmoplasia in the stroma.

This is the first study to evaluate maspin expression in BCC of the skin. No statistical association between maspin and classical pathological features was observed. Interestingly, we observed a remarkable difference in the distribution of maspin in metatypical carcinomas and nodular BCCs. While the first showed diffuse cytoplasmic immunoreactivity, even in the borders of cell cords and clusters, the later revealed a distinctive distribution in the center of cell nodules. Again, this militates against a role of maspin on the blockage of invasion by neoplastic cells. Remarkably, we observed that maspin was consistently expressed in cells showing squamous differentiation in all BCCs evaluated here. Based on these observations and on the higher expression of maspin in well differentiated SCCs, we again hypothesize that maspin plays a role in terminal squamous differentiation. Again, experimental studies should be carried out in order to definitively clarify this issue.

In contrast to other tumor suppressor genes, mutations and deletions of the maspin gene are exceedingly rare and do not seem to result in the loss of maspin expression [5, 6, 9]. Recently Domann et al. [5] and Futscher et al. [6] shed light on the regulation of the tissue specific distribution of maspin as well as in the putative mechanisms of downregulation of maspin expression in human neoplasms [5, 6]. These studies demonstrated that the methylation status of the CpG island of the maspin gene promoter is inversely correlated with maspin expression: while blood lymphocytes, skin fibroblasts, bone marrow cells, heart muscle and kidney epithelial cells do not express maspin and have dense methylation of maspin gene promoter; airway epithelium, breast and prostate "epithelial" cell lines as well as skin and oral keratinocytes lack methylation of maspin gene promoter and consistently express maspin [5, 6]. Most importantly, Futscher et al. [6] also showed that maspin expression-immortalized fibroblasts can express maspin after treatment with a DNA methyltransferase inhibitor 5-aza-2′-deoxycytidine [6].

Further regulation of tissue specificity of maspin expression may be related to the presence of an hormonal responsive element (HRE) in the maspin gene promoter, which downregulates the transcription of this gene [35, 39]. It has been shown that activated androgen receptors (ARs) can bind to the HRE and block the transcription of maspin in prostate cancer cell lines [35]. ARs are ubiquitously distributed in the human body, and it would be tempting to speculate that ARs play a role in the regulation of maspin expression in cutaneous structures [2, 3, 8, 29]. In the skin ARs are consistently observed in seboblasts and in a variable proportion of sebocytes [3, 8, 29]. In other cutaneous structures, such as dermal papilla of hair follicles, hair follicle epithelial cells, eccrine and apocrine sweat glands, and keratinocytes, ARs show highly variable expression [3, 8, 29]. The discrepancies observed in numerous studies may be related to the differences in the tissue samples (frozen vs. formalin-fixed), immunohistochemical methods, and antibodies used to assess their distribution [2, 3, 8, 29]. Notably, in contrast to what have been described in prostate carcinoma cell lines, in which maspin expression is negatively regulated by ARs [35], mature sebocytes concurrently express maspin and ARs. Moreover, up to 60% of BCCs expresses ARs [3] and also express maspin. Thus the role of ARs in the regulation of maspin expression in normal skin and cutaneous neoplasms remains unsettled.

In conclusion, we described maspin expression in normal skin, cutaneous appendages, SCCs, and BCCs. We demonstrated that maspin is consistently expressed in the cytoplasm of keratinocytes of suprabasal, granular, and spinous layers, in terminally differentiated sebaceous cells, and in the inner root sheath cells of hair follicles. Interestingly, a nuclear distribution of maspin was observed in the nuclei of basal cells of sweat glands and occasional differentiated sebaceous cells as well as in two BCCs and one SCC. In SCCs maspin was strongly expressed in cells showing features of terminal squamous differentiation; in contrast, nodular BCCs show a peculiar distribution of maspin, while metatypical carcinoma cells were strongly decorated by maspin.

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