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Original Article

Expression of Snail transcription factor in prostatic adenocarcinoma in Egypt: correlation with Maspin protein expression and clinicopathologic variables

Ashraf Ishak Fawzy[1*], Mariana Fathy Gayyed[1*], Gamal Abd Elhamid Elsaghir[2], Mohamed Salah Elbadry[3]

[1]Department of Pathology, Faculty of Medicine, Minia University, El-Minia, Egypt; [2]Department of Urology, South Valley University, Qena, Egypt; [3]Department of Urology, Minia University Hospital, Minia University, El-Minia, Egypt. [*]Equally contributors.

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Abstract: Background: Snail transcription factor and Maspin tumor suppressor serpin are involved in the regulation of progression, invasion and metastasis of many human malignancies. However, there is very limited data in the literature about their role in prostatic adenocarcinoma. The present study was designed to investigate Snail and Maspin expression, their interrelationship and their relationship to different clinicopathologic variables in clinically detectable prostatic adenocarcinoma. Material and methods: Tissue sections from 110 resected prostatic lesions distributed as 80 cases of prostatic adenocarcinoma and 30 cases of benign prostatic hyperplasia (BPH) were evaluated for Snail and Maspin proteins expression by immunohistochemistry. Results: Snail protein expression was detected in 53.8% of prostatic adenocarcinomas versus none of BPH cases (p = < 0.001). A significant positive correlation of Snail expression to cancer grade (p = 0.015), lymph node metastasis (p = 0.026) and pTNM stage (p = 0.036). Maspin expression was detected in 36.6% of prostatic adenocarcinomas versus 93.3% of BPH cases (p = < 0.001). A significant negative correlation of Maspin expression to cancer grade (p = 0.007) and lymphovascular invasion (p = 0.017). Also detected was a significant negative relationship between Snail and Maspin expression in cancer cases under investigation (p = 0.002). Conclusion: Snail immunohistochemical expression can be promising as a potential prognostic biomarker in prostatic adenocarcinoma since it was significantly associated with clinicopathologic variables of progressive disease. A potential role for Snail in regulating Maspin expression is suggested based on the finding of negative association between Snail and Maspin expression in prostatic adenocarcinoma.

Keywords: Benign prostatic hyperplasia, immunohistochemistry, Maspin, prostatic adenocarcinoma, Snail, clinicopathologic variables

Introduction

Prostate cancer is the second most frequently diagnosed cancer in men worldwide, the sixth leading cause of cancer death in men and the fifth most common cancer overall [1]. Invasion and metastasis of the cancer are the primary factors affecting the survival rate of patients [2]. Although many trials have been made to understand the molecular mechanisms underlying tumor invasion and metastasis, this issue is still largely poorly defined.

One recently described mechanism is epithelial-mesenchymal transition (EMT) which refers to a process in which the epithelial cells lose their epithelial characteristics and gain migratory and invasive properties of mesenchymal cells [3]. This process was originally described in the context of embryologic development and morphogenesis, then in wound healing, tissue regeneration and fibrosis and more recently in cancer progression where it was proposed to be the first necessary step for invasion-metastasis cascade in epithelial malignancy [4]. EMT can be induced by a variety of signaling pathways characterized by one common effect which is the transcriptional repression-mediated down-regulation of E-cadherin adhesion molecule which is considered the hallmark of EMT [5]. Among those transcriptional repressors, Snail superfamily of zinc-finger transcription factors remains the most important and includes Snail (also known as SNAI1, snail

Table 1. Tumor and Patients Characteristics

Characteristics	N	(%)
Age at diagnosis		
Range	48–78 years	
Mean	64.4 ± 6.9 years	
Histopathological diagnosis		
Benign prostatic hyperplasia (BPH)	30	(27.3)
Prostatic Adenocarcinoma	80	(72.7)
Tumor differentiation (for prostatic adenocarcinoma)		
G1: Well differentiated (Gleason 2-4)	20	(25)
G2: Moderately differentiated (Gleason 5-6)	34	(42.5)
G3-4: Poorly differentiated/undifferentiated (Gleason 7-10)	26	(32.5)
pT status		
T2	41	(51.3)
T3	32	(40)
T4	7	(8.8)
pN status		
N0	68	(85)
N1	12	(15)
pTNM stage		
II	38	(47.5)
III	26	(32.5)
IV	16	(20)
LVI		
Negative	56	(70)
Positive	24	(30)
PNI		
Negative	35	(43.8)
Positive	45	(56.3)

pT, tumor stage; pN, lymph node status; M, distant metastasis. N = number; (%) = percentage; LVI, lymphovascular invasion; PNI, peineural invasion.

homolog 1, SNA, SNAH, SLUGH2, dJ710H13.1), Slug (SNAI2) and Smuc (SNAI3) [6]. However, Snail is the most important of this family since it plays a pivotal role in EMT triggering [7]. Snail overexpression and its prognostic value have been demonstrated in several human cancers [8-10]. But for prostatic adenocarcinoma, most of the data available in the literature resulted from studying Snail expression in cancer cell lines and there is very limited data concerning Snail expression and its association with the clinicopathologic variables in surgical biopsy specimens.

Maspin (Mammary Serine Protease Inhibitor) is a 42 kDa tumor suppressor member of the serine protease inhibitor family, originally discovered in normal mammary epithelium but reduced or absent in breast carcinomas [11]. The protein is encoded by a gene on chromosome 18q21.3-q-23, along with other serpin genes such as squamous cell carcinoma antigens 1 and 2, PAI-2, and headpin [12]. Maspin is normally expressed in the epithelium of several human organs including breast, prostate, thymus, testis, small intestine, and colon [13]. It is found localized to the cytoplasm, secretory vesicles and the cell membrane interface with the extracellular matrix [11]. Maspin is classified as a class II tumor suppressor, since it is downregulated or silenced in cancer cells by hypermethylation unlike class I tumor suppressors which are downregulated by mutation [14]. It suppresses tumor growth and metastasis *in vivo* and inhibits basement membrane invasion *in vitro* which could be related to Maspin's effects on tumor cell adhesion, motility, survival and angiogenesis [11, 15, 16]. However, much controversy exists in the literature concerning Maspin tumor suppressive effects, expression pattern and its prognostic value in different human clinical cancer specimens including prostatic cancer [12, 17, 18].

The present study was designed to investigate the immunohistochemical expression of Snail and Maspin proteins in prostatic adenocarcinoma, their relationships to clinicopathologic variables as well as their relationship to each other. Also targeted was highlighting biomarkers expression in BPH specimens and in HGPIN foci as well as normal prostatic tissue included in cancer cases.

Table 2. Snail Immunostaining and Clinicopathological Variables in Prostatic Adenocarcinoma

	N	Negative staining n (%)	Positive staining n (%)	*p*
Age (years)				
Range		55–78	56–77	0.494
(Mean ± St. deviation)		(65.2 ± 6.1)	(66.2 ± 6.4)	
Tumor differentiation				
G1	20	14 (70.0%)	6 (30.0%)	0.015
G2	34	16 (47.1%)	18 (52.9%)	
G3-4	26	7 (26.9%)	19 (73.1%)	
pT status				
T2	41	23 (56.1%)	18 (43.9%)	0.178
T3	32	11 (34.4%)	21 (56.6%)	
T4	7	3 (42.9%)	4 (57.1%)	
pN status				
N0	68	35 (51.5%)	33 (48.5%)	0.026
N1	12	2 (16.7%)	10 (83.3%)	
pTNM stage				
II	8	23 (60.5%)	15 (39.5%)	0.036
III	26	10 (38.5%)	16 (61.5%)	
IV	16	4 (25.0%)	12 (75.0%)	
LVI				
Negative	56	29 (51.8%)	27 (48.2%)	0.149
Positive	24	8 (33.3%)	16 (66.7%)	
PNI				
Negative	35	18 (51.4%)	17 (48.6%)	0.413
Positive	45	19 (42.2%)	26 (57.8%)	

Material and methods

Study design

The present study was carried out on paraffin blocks of formalin-fixed tissue sections of 110 prostatic specimens distributed as 80 cases of prostatic adenocarcinoma and 30 cases of benign prostatic hyperplasia (BPH). These specimens were retrieved from the archives of Histopathology Lab of Department of Pathology, Minia Faculty of Medicine and were obtained from randomly selected patients who underwent transurethral resection prostatic biopsies and radical prostatectomy for clinically detectable prostatic lesions in the Urology Department, Minia Faculty of Medicine during the period from 2006-2011. The presence of distant metastases was excluded in cancer cases by abdominal computerized tomography (CT) scans, X-rays of the lungs and bone scans prior to the surgical intervention. The histopathological diagnosis of all specimens and grading of cancer cases were revised by two histopathologists (A.I.F and M.F.G). Grading of cancer cases was done primarily according to Gleason's grading system and then cases were grouped according to corresponding WHO grading system considering glandular differentiation. Staging was based on the Tumor-Node-Metastasis system [2]. Twenty four specimens of cancer cases harbored residual benign prostate tissue and 15 specimens had foci of high-grade prostate intraepithelial neoplasia (HGPIN). The age of patients ranged from 48-78 years with mean age 64.4 ± 6.9 years. The patient and tumor characteristics of investigated cases were shown in **Table 1**.

Immunohistochemical staining

Immunohistochemical staining was performed on 4-μm thick sections. These sections were deparaffinized in xylene, rehydrated in descending grades of alcohol, and washed in phosphate buffered saline (PBS) (pH 7.2). Sections were incubated with 3% hydrogen peroxide in methanol for 15 minutes after heat-induced antigen retrieval (five 3-min microwave oven passages at 750 W in 10 mM sodium citrate buffer, pH 6.0). Then, sections were incubated for 60 minutes at room temperature with primary antibodies against Snail (dilution 1:50, rabbit polyclonal, Abcam, Cambridge, UK) and Maspin (dilution 1:100, monoclonal mouse, clone EAW24, Labvision, Thermo Scientific Inc, Fremont, CA, USA). After washing in PBS, sections were incubated with biotin-labeled secondary antibody and then with streptavidin-horseradish peroxidase using the DAKO universal LSAB2/HRP kit (DAKO, Glostrup, Denmark) at room temperature for 30 minutes for each step. DAB (3,3 diaminobenzidine) was used as chromogen and hematoxylin as the

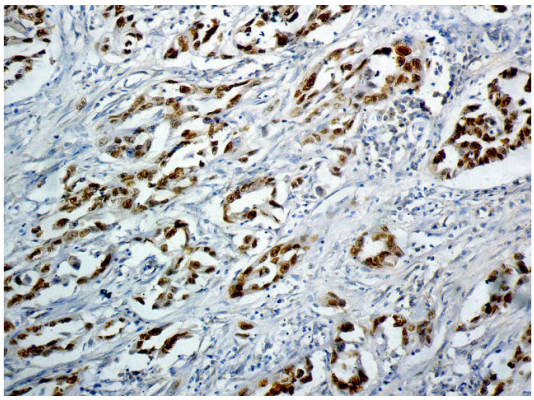

Figure 1. Moderately differentiated prostatic adenocarcinoma exhibiting reduced nuclear positivity for Snail expression.

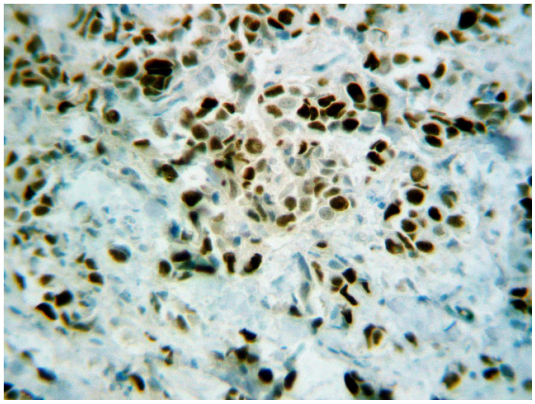

Figure 2. Poorly differentiated prostatic adenocarcinoma showing strong nuclear immunostaining of Snail expression.

nuclear counterstain. Negative control was performed by omission of primary antibodies and replacement by PBS. Positive control for Snail was placental tissue while that for Maspin was normal prostate tissue.

Interpretation of IHC results

Positive immunostaining for Snail was nuclear while that of Maspin was cytoplasmic ± nuclear. Sections were considered as positive when at least 40% and 49% of tumor cells were stained for Maspin and Snail; respectively [19, 20].

Statistical analysis

The statistical analyses were performed using SPSS for Windows, version 12.0 (SPSS Inc., Chicago, IL). Chi-square and Fisher's exact tests were used when appropriate to assess the relationships between biomarkers and clinicopathological variables of included tumors. Two-sided *P*-values of < 0.05 were considered significant.

Results

Snail immunohistochemical expression

Positive nuclear immunostaining for Snail (≥ 49%) was detected in 43 out of 80 prostatic adenocarcinomas (53.8%) versus none of BPH cases (p = < 0.001). In HGPIN foci included in cancer cases, focal weak Snail expression was noted in the secretory cells within these foci. On the contrary, benign prostatic tissues included in prostatic adenocarcinoma specimens were completely negative irrespective of the level of the biomarker expression within the malignant tissue. In prostatic adenocarcinoma, our study demonstrated a significant positive association between the rate of positive immunoreactivity for Snail and higher tumor grades since 6 out of 20 well differentiated (G1) tumors (30%), 18 out of 34 moderately differentiated (G2) tumors (52.9%) and 19 out of 26 poorly differentiated to undifferentiated (G3-4) tumors (73.1%) were positively immunostained for Snail (X^2 = 8.454, p = 0.015). Also, Snail immunoreactivity was significantly associated with lymph node metastasis as the rate of Snail positive immunostaining was significantly higher in prostatic adenocarcinomas associated with lymph node metastasis (N1) (10/12 cases; 83.3%) when compared with those without lymph node metastasis (N0) (33/68 cases; 48.5%) (X^2 = 4.970, p = 0.026). The present study also demonstrated a positive association between positive immunostaining for Snail and higher pTNM stages. The rate of positive immunostaining for this biomarker was 15 out of 38 stage II carcinomas (39.5%), 16 out of 26 stage III tumors (61.5%) and 12 out of 16 stage IV tumors (75%) (X^2 = 6.656, p = 0.036). No significant relationship was observed between Snail expression and age (p = 0.494), pT (p = 0.178), LVI (p = 0.149) and PNI (p = 0.413). (**Table 2**, **Figures 1** and **2**).

Maspin immunohistochemical expression

Positive immunoreactivity for Maspin (≥ 40%) was detected in 29 out of 80 prostatic adeno-

Table 3. Maspin Immunostaining and Clinicopathological Variables in Prostatic Adenocarcinoma

	N	Negative staining n (%)	Positive staining n (%)	*P*
Age (years)				
Range		56–77	55–78	0.936
(Mean ± St. deviation)		(65.6 ± 5.9)	(65.7 ± 6.4)	
Tumor differentiation				
G1	20	7 (35.0%)	13 (65.0%)	0.007
G2	34	24 (70.6%)	10 (29.4%)	
G3-4	26	20 (76.9%)	6 (23.1%)	
pT status				
T2	41	23 (56.1%)	18 (43.9%)	0.344
T3	32	23 (71.9%)	9 (28.1%)	
T4	7	5 (71.4%)	2 (28.6%)	
pN status				
N0	68	42 (61.8%)	26 (38.2%)	0.379
N1	12	9 (75.0%)	3 (25.0%)	
pTNM stage				
II	38	20 (52.6%)	18 (47.4%)	0.143
III	26	19 (73.1%)	7 (26.9%)	
IV	16	12 (75.0%)	4 (25.0%)	
LVI				
Negative	56	31 (55.4%)	25 (44.6%)	0.017
Positive	24	20 (83.3%)	4 (16.7%)	
PNI				
Negative	35	20 (57.1%)	15 (42.9%)	0.278
Positive	45	31 (68.9%)	14 (31.1%)	

carcinomas (36.6%) versus 28 out of 30 BPH (93.3%) (p = < 0.001). In the latter, more than 80% of epithelial cells were immunostained and even those cases scored as negative were definitely immunostained but in less than 40% of their epithelial lining. As regard the pattern of Maspin immunostaining, it also varied from benign to malignant lesions. In benign prostatic tissue, the basal cell cytoplasm and nuclei were strongly and uniformly immunoreactive for Maspin. The secretory cells generally show less intense cytoplasmic staining than basal cells; however, focally intense cytoplasmic reaction was noted in secretory cells particularly in the periurethral prostatic glands. In HGPIN, basal cells retain their immunostaining pattern as in benign prostatic glands but secretory cells, unexpectedly and paradoxically, express more intense cytoplasmic reaction than their counterparts in benign glands. In prostatic adenocarcinoma, there is loss of basolateral Maspin expression corresponding to loss of basal cell layer. The malignant secretory cells show biphasic immunostaining pattern; initially more differentiated tumors often retain Maspin expression and displayed immunostaining pattern indistinguishable from HGPIN but less differentiated tumors progressively showed reduced Maspin expression so that the majority of high-grade tumors exhibit little or no cytoplasmic immunoreactivity. Accordingly, the rate of positive immunoreactivity for Maspin was demonstrated to be inversely correlated with histological grade of prostatic adenocarcinomas included in our study where biomarker immunoreactivity was detected in 13 out of 20 G1 tumors (65%), 10 out 34 G2 tumors (29.4%) and 6 out of 26 G3 tumors (23.1%) (X^2 = 9.794, p = 0.007). Also noted is that maspin expression was negatively associated with lymphovascular invasion (LVI) since maspin expression was demonstrated in 4 out 24 cancer cases with LVI (16.7%) versus 25 out of 56 cases without LVI (44.6%) (X^2 = 5.690, p = 0.017). Otherwise, no significant relationship was detected between Maspin expression and any other clinicopathologic variables in prostatic adenocarcinomas including age (p = 0.936), pT (p = 0.344), pN (p = 0.379), pTNM stage (p = 0.143) and PNI (p = 0.278). (**Table 3**, **Figures 3** and **4**).

The relationship between Snail and Maspin immunoreactivity

The present study demonstrated a significant negative relationship between Snail and Maspin immunoreactivity in prostatic adenocarcinoma since among 43 cases positive for Snail immunostaining, only 9 cases (20.9%) were positive for Maspin while 34 cases (79.1%) were negative (X^2 = 9.442, p = 0.002). (**Table 4**).

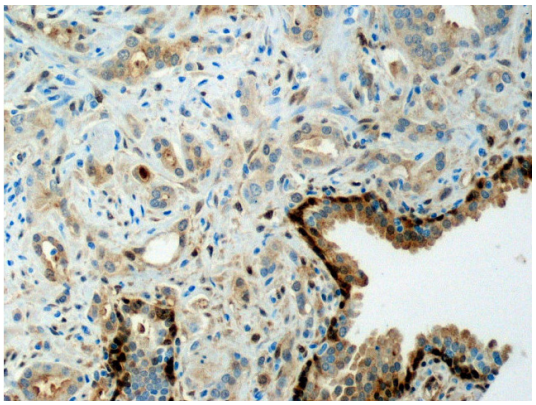

Figure 3. Maspin expression in HGPIN (right and bottom) displaying both nuclear and cytoplasmic immunostaining in basal cells and more intense cytoplasmic reaction in the secretory cells. While Maspin expression in poorly differentiated prostatic adenocarcinoma (left and top) exhibiting little or no cytoplasmic immunoreactivity.

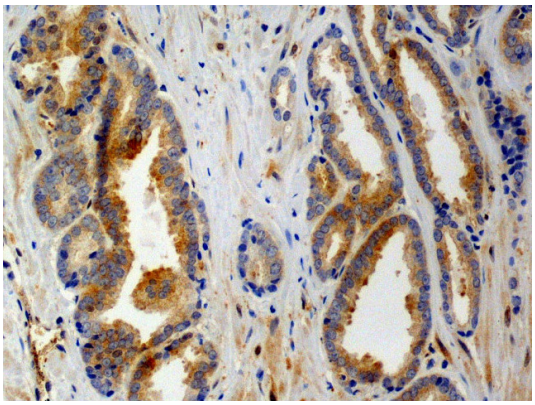

Figure 4. Maspin expression in moderately differentiated prostatic adenocarcinoma showing strong cytoplasmic reaction in the malignant secretory cells. An immunostaining pattern indistinguishable from HGPIN.

Discussion

EMT is a rapid and often reversible change in the cell phenotype associated with loss of epithelial characteristics and acquisition of mesenchymal characteristics. The epithelial cells lose their adhesion structures including adherens junctions and desmosomes, modulate their polarity and rearrange their cytoskeleton so that intermediate filaments revert to vimentin from keratins. Consequently, the cells become motile with migratory and invasive capabilities and show greater resistance to apoptosis in consistency with the acquired mesenchymal cell phenotype [5]. Snail protein is considered the master regulator of EMT and consecutively of tumor progression. It exerts its main function in the induction of EMT through repression for E-cadherin transcription by binding to E-box elements found in the proximal E-cadherin promoter [3]. More recent study has defined a novel role for Snail in influencing EMT through downregulation of integrins responsible for cell adhesion to extracellular matrix via MAPK pathway, thereby promoting cell detachment, migration capabilities and metastatic potential [7]. Besides its role in EMT and tumor invasion, Snail upregulation has been linked to other cancer hallmarks such as promotion of cell proliferation, resistance to apoptosis, evasion of immunosurveillance and adoption of tumor initiating or cancer stem cell characteristics [5]. Consistent with these biological functions, Snail overexpression as well as its association with tumor progression or poor outcome have been shown in a wide variety of human malignancies including breast [9], gastric [10], pancreatic [8], urinary bladder [20], and oral [6] carcinomas. Limited data is available in the literature about Snail expression in prostatic adenocarcinoma and its prognostic value in human clinical specimens. The present study demonstrated complete absence of Snail expression in BPH as well as normal prostatic tissue while focal weak expression was noted in HGPIN foci included in cancer cases. As regard prostatic adenocarcinomas, Snail overexpression was detected in more than half of our investigated cases and it was significantly positively associated with clinicopathologic variables of progressive or advanced disease including higher histologic grades, nodal metastasis and higher pTNM stage. These findings suggest that Snail is essentially a biomarker for prostatic cancer progression rather than cancer initiation and point to its potential prognostic value in prostatic adenocarcinomas. Up to our best knowledge, only one study is available in the literature reported by Heeboll et al. [21] regarding immunohistochemical expression of Snail in benign and malignant prostatic lesions and its relationship to clinicopathological variables. Several points of concordance are present between the results of the present study and those reported by Heeboll [21] and his colleagues concerning BPH and prostatic adenocarcinoma. In the former, those investigators have found absence of Snail overexpression in

Table 4. Snail and Maspin immunostaining in BPH and Prostatic adenocarcinoma

	N	Snail immunostaining			Maspin immunostaining		
		Negative n (%)	Positive n (%)	*P-value*	Negative n (%)	Positive n (%)	*P-value*
BPH	30	0	0	<0.001	2 (6.7%)	28 (93.3%)	<0.001
Prostatic adenocarcinoma	80	37 (46.3%)	43 (53.8%)		51 (63.8%)	29 (36.3%)	

all included cases. In the latter, they have reported very close rate of snail overexpression, significant positive association of Snail immunohistochemical expression with tumor grade namely Gleason's score and lack of correlation with pT, Nevertheless, those investigators have found that snail expression was correlated neither to metastasis at time of diagnosis, risk of or time to recurrence nor to cancer prognosis as a consequence. Concerning Snail expression in normal prostatic tissue included in cancer cases and in discordance with the study by Heeboll et al. [21] who have reported Snail overexpression in 21% of their cases, no snail overexpression was noted in our investigated cases. In this respect, our finding is supported by a very recent study by Neal et al. [22] who have reported that normal prostatic cells failed to express any detectable level of Snail by means of RT-PCR and Western blot analysis. Another point of discordance is that related to Snail expression in HGPIN since biomarker expression was only focal and weak in HGPIN foci included in our cancer cases while Heeboll [21] and his colleagues have reported high levels of Snail expression in 7% of HGPIN specimens included in their study. This discrepancy may be partly attributed to different methodology as well as different sensitivity and specificity of utilized antibodies. There is one more study by Odero-Marah et al. [23] which has shown Snail expression by immunohistochemistry to be increased with prostate cancer progression from benign to bone metastatic human clinical specimens without further details since this study was primarily designed to study EMT-associated molecular changes in human prostatic cancer cell lines and in bone metastasis induced by these cell lines in animal models. Otherwise, all other studies available in the literature are molecular-based and utilized prostatic cancer lines with no human clinical specimens. However, those studies have defined the role of Snail in EMT and demonstrated Snail overexpression in concordance with prostatic cancer progression and metastasis [7, 22, 24].

The earliest studies on Maspin demonstrate its ability to inhibit tumor cell growth, invasion and metastasis in breast and prostate cancer cell lines [11]. Since then, many studies have been made to clarify the possible mechanisms underlying Maspin's tumor suppressive functions. Maspin has been shown to enhance cell adhesion and block cell migration and metastasis through several mechanisms including: (1) alteration of integrin profile of the cells; thereby increasing cell adherence to fibronectin and reducing invasion through a fibronectin/gelatin matrix, (2) interaction with various components of the extracellular matrix (ECM), including collagens I and III; thereby enhancing cell adhesion to ECM, and (3) inhibition of pericellular proteolysis via reducing cell surface-associated urokinase-type plasminogen activator (uPA)/ urokinase-type plasminogen activator receptor (uPAR) complex by inducing its internalization leading to reduction of tumor cell invasion [25]. Also, Maspin may function as an angiogenesis inhibitor since it was found to reduce tumor microvessel density through blocking fibroblast growth factor and vascular endothelial growth factor-mediated endothelial cell migration, mitogenesis and tube formation [15]. Maspin has also been shown to increase susceptibility of breast and prostate cancer cells to induced apoptosis mediated by upregulation of the proapoptotic protein *bax* [16]. Nevertheless, there is much controversy about the demonstration of Maspin's tumor-suppressive effect in human clinical cancer specimens. While many studies have been demonstrated such effect in some organs [17, 26, 27], others were not able to demonstrate this effect [18, 28]. Moreover, some studies show an association of Maspin expression with a more aggressive disease [12, 13, 29]. Such discrepancy between studies might be related to different subcellular location and expression patterns of Maspin, different cancers, or even the same cancer with different genetic backgrounds on one side and to the difference in antibodies used, methods of immunohistochemistry, criteria of positive staining and statistical analysis

on the other. As regard prostatic adenocarcinoma, the present study in concordance with earlier reports by Machtens et al. [19] and Pierson et al. [30] has demonstrated inverse relationship between Maspin expression and tumor grade. The former investigators have also demonstrated significant association of Maspin expression with lower tumor stages and increase recurrence–free survival. On the contrary, a study by Zou et al., [18] has reported positive correlation of Maspin expression to tumor grade with no relationship to progression-free survival. Nevertheless, none of the above investigators has examined the relationship of Maspin expression with LVI unlike the present study which has demonstrated a significant association between loss of Maspin expression and the presence of LVI. Such finding can be correlated to Maspin's ability to inhibit tumor cell invasion and metastasis.

Down-regulation of Maspin during cancer progression has been mediated by several mechanisms including methylation of Maspin promoter [14] as well as binding of Maspin promoter by inhibitory transcription factors like mutant p53 and androgen receptor (AR) [18, 19]. The present study has shown a highly significant negative relationship between Snail and Maspin expression; suggesting a potential role for Snail in regulating Maspin expression. Our finding is in line with a very recent study in which transfection of Snail into prostate cancer cell lines has led to inhibition of Maspin promoter activity and expression leading to increased cancer cell migration and invasion while knockdown of Snail in cancer cells has led to up-regulation of Maspin expression, concomitant with decreased migration [22]. Therefore, therapeutic targeting of Snail could be beneficial to restore Maspin expression and functions as tumor suppressor to prevent prostate cancer progression.

In conclusion, the present study identifies Snail as a potential prognostic biomarker in prostatic adenocarcinoma since Snail overexpression was significantly positively associated with clinicopathologic variables of progressive or advanced disease. Also detected is a significant negative relationship between Snail and Maspin expression; suggesting a potential role for Snail in regulating Maspin expression. Therapeutic targeting of Snail could be promising in prevention of prostate cancer progression through re-induction of Maspin expression and restoration of its tumor suppressor functions.

Address correspondence to: Dr. Mariana Fathy Gayyed, Department of Pathology, Faculty of Medicine, Minia University, Minia, Egypt, 61111. Phone: (002) 01001143941; E-mail: mariana.gaid@mu.edu.eg; marianafathy@yahoo.com

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