

Prostatic Carcinogenesis: More Insights

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Abstract

Background: Prostatic carcinoma ranks as the second most common malignant tumor and the fifth cause of cancer-related deaths in men. Many studies now focus on the different molecules involved in prostatic carcinogenesis. Maspin and prohibitin (PHB) are suggested to play crucial roles in the development and progression of many cancers; however, their roles in prostatic carcinogenesis have not been fully elucidated. **Aim:** This work was designed to study the immunohistochemical expression of maspin and PHB in prostatic carcinoma in comparison to their expression in benign prostatic hyperplasia (BPH) to give more insights about their roles in prostatic carcinogenesis. **Materials and Methods:** Archival blocks of 30 cases of prostatic adenocarcinomas and 15 cases of BPH were subjected to histopathological examination and immunohistochemical evaluation of maspin and PHB expression. **Results:** Maspin showed higher expression in prostatic carcinoma (88.9% of cases) compared to BPH (20% of cases). PHB expression was detected only in prostatic carcinoma (84.4% of cases), while all cases of BPH were negative. The expression of both maspin and PHB showed statistically significant increase with increasing Gleason score ($P = 0.0125$ and 0.0065 respectively). **Conclusions:** Overexpression of maspin and PHB in prostatic carcinoma reflects their vital roles in prostatic carcinogenesis. Their upregulation with increasing Gleason score indicates their prognostic significance. Moreover, PHB may differentiate between prostatic carcinoma and BPH being expressed only by malignant cells.

Keywords: Gleason score, maspin, prognosis, prohibitin, prostatic carcinoma

INTRODUCTION

Prostatic carcinoma is a major health problem as it is considered the second most common malignancy among men and the fifth leading cause of cancer-related death worldwide.^[1,2] It results from a combination of genetic and environmental factors that alter key cellular processes and involves multiple cellular pathways and molecules implicated in its initiation and progression, however, the specific underlying mechanisms of prostatic carcinogenesis are still unrevealed.^[3,4]

Maspin (mammary serine protease inhibitor) and prohibitin (PHB) are important key molecules involved in different cellular mechanisms related to carcinogenesis. Maspin is a member of the serine protease inhibitor/noninhibitor superfamily (serpin), located on chromosome 18q21.3–q23. Interestingly, it was described to be overexpressed in some cancers including pancreatic, gallbladder, colorectal, and thyroid cancers, while downregulated in other cancers including breast and gastric carcinomas as well as melanomas.^[5,6]

PHB is a high molecular weight protein located in the mitochondria, nucleus, and plasma membranes^[7] and has been

described to be involved in multiple processes controlling the development and growth of different organ cancers. Similar to maspin, PHB overexpression was described in some cancers involving the cervix, esophagus, stomach, breast, lung, bladder, thyroid, and ovary, while others such as gliomas showed downregulation.^[8]

Aim of the work

This work was designed to study the immunohistochemical expression of maspin and PHB in prostatic carcinoma in comparison to their expression in benign prostatic hyperplasia (BPH) to give more insights about their roles in prostatic carcinogenesis.

MATERIALS AND METHODS

This study was carried out on paraffin blocks of formalin-fixed tissue sections of 45 prostatic specimens including 30 cases

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of prostatic adenocarcinoma and 15 cases of BPH. These specimens were retrieved from the archives of the Department of Pathology, Faculty of Medicine, Tanta University, during the period from 2012 to 2015. None of the studied patients received neoadjuvant chemotherapy, radiotherapy, or hormonal therapy. The study was approved by the Research Ethics Committee of the Faculty of Medicine, Tanta University.

Histopathological study

The histopathological diagnosis of the studied specimens was revised, and prostatic carcinoma cases were graded according to the Gleason grading system.^[9] Gleason scores 2–4 were classified as well differentiated, 5–6 as moderately differentiated, and 7 or more as poorly differentiated prostatic carcinoma.^[10]

Immunohistochemistry

Immunohistochemical staining was performed using the UltraVision Detection Kit (TP-015-HD, Lab Vision, USA), according to the manufacturer's protocol. After deparaffinization and heat pretreatment, sections were incubated for 10 min with Ultra V block to prevent nonspecific background staining, followed by rinsing the sections with PBS. Afterward, an overnight incubation was done in a humidity chamber with mouse monoclonal anti-maspin (E-10) antibody (clone sc-166260, Santa Cruz Biotechnology, Inc.) at a dilution 1:100, and mouse monoclonal anti-PHB (E-5) antibody (clone sc-377037, Santa Cruz Biotechnology, Inc.) at a dilution 1:100, followed by washing in PBS. Sections were then covered with 4–5 drops of UltraVision Biotinylated Goat Anti-Polyvalent secondary antibody, incubated at room temperature for 10 min, then washed in PBS, followed by incubation with streptavidin-peroxidase solution for 10 min at room temperature, then rinsing with PBS. Sections were then covered for 15 min by adding one drop of 3,3'-diamino-benzidine-tetra-hydrochloride (DAB) chromogen mixed with 2 ml of DAB substrate [Figure 1]. Finally, sections were counterstained with Mayer's hematoxylin, dehydrated in alcohol, and mounted in di-n-butyl-phthalate-polystyrene-xylene. As positive controls, sections from human tonsil (for maspin) and sections from human ovarian tissue (for PHB) were used. Negative controls were prepared by omission of the primary antibodies.

Evaluation of maspin and prohibitin immunohistochemical staining

Distinct granular cytoplasmic staining for maspin and cytoplasmic and/or nuclear staining for PHB were considered to indicate positive immunoreactivity [Figure 2]. The immunohistochemical score (IHS) was used for maspin and PHB immunohistochemical evaluation by means of light microscopy by examination of 10 high-power fields ($\times 400$) in each slide, and the average IHS score was calculated by combining the quantity score (percentage of positive-stained cells) with the staining intensity score. The quantity score ranges from 0 to 4, that is, 0, no immunostaining; 1, 1%–10% of cells are stained; 2, 11%–50% are positive; 3, 51%–80%

are positive; and 4, $\geq 81\%$ of cells are positive. The staining intensity was scored as: 0 (negative), 1 (weak), 2 (moderate), and 3 (strong). Raw data were converted to IHS by multiplying the quantity score (0–4) by the staining intensity score (0–3), with a range from 0 to 12. An IHS of 9–12 was considered a strong (+3); 5–8, moderate (+2); 1–4, weak (+1); and 0, negative immunoreactivity.^[11]

Statistical analysis

Statistical analysis was performed with the MedCalc[®] Version 15.6.1 (MedCalc Software bvba, Ostend, Belgium). The Chi-square test was used for analysis of the differences in maspin and PHB immunohistochemical expression between the different grades of prostatic carcinoma. $P < 0.05$ was considered statistically significant.

RESULTS

Histopathological results

The studied prostatic carcinoma cases (30 cases) included 8 cases (26.7%) of well differentiated, 12 cases (40%) of moderately differentiated, and 10 cases (33.3%) of poorly differentiated carcinoma.

Immunohistochemical analysis of maspin expression

Positive maspin expression was detected in 3/15 (20%) cases of BPH, the positivity was seen only in the basal cells. In the studied prostatic carcinomas, 21/30 (70%) of cases showed positive maspin immunoreactivity. The highest maspin expression was observed in poorly differentiated carcinomas (10/10 [100%] of cases), followed by moderately differentiated carcinomas (8/12 [66.7%] of cases), and finally well-differentiated carcinomas (3/8 [37.5%] of cases), with a statistically significant difference between the different grades of the studied tumors ($P = 0.0125$). The immunohistochemical expression of maspin in the studied prostatic carcinoma cases is shown in Table 1 and Figure 1.

Immunohistochemical analysis of prohibitin expression

PHB expression was detected in 21/30 (70%) of the studied prostatic carcinomas, while all the studies cases of BPH showed negative expression.

Within the studied carcinomas, the highest PHB expression was detected in poorly differentiated carcinomas (9/10 [90%] of cases), followed by moderately differentiated carcinomas (8/12 [66.7%] of cases), and finally well-differentiated carcinomas (4/8 [50%] of cases). PHB expression showed highly significant increase with increasing Gleason score ($P = 0.0065$). The immunohistochemical expression of PHB in the studied cases is shown in Table 2 and Figure 2.

DISCUSSION

Prostatic carcinoma is the most frequently diagnosed cancer in males and the second leading cause of cancer-related morbidity and mortality.^[12] Although the precise underlying mechanisms of prostatic carcinogenesis have not been fully

Table 1: Maspin expression in the studied prostatic carcinoma cases

Maspin IHS	Gleason score			Total (%)	χ^2	P
	Well differentiated, n (%)	Moderately differentiated, n (%)	Poorly differentiated, n (%)			
0	5 (62.50)	4 (33.30)	0	9 (30.0)	16.242	0.0125*
+1	3 (37.50)	2 (16.70)	2 (20.00)	7 (23.3)		
+2	0	4 (33.30)	2 (20.00)	6 (20.0)		
+3	0	2 (16.70)	6 (60.00)	8 (26.7)		
Total	8 (26.70)	12 (40.00)	10 (33.30)	30		

*Significant difference. IHS: Immunohistochemical score

Table 2: Prohibitin expression in the studied prostatic carcinoma cases

Prohibitin IHS	Gleason score			Total, n (%)	χ^2	P
	Well differentiated, n (%)	Moderately differentiated, n (%)	Poorly differentiated, n (%)			
0	4 (50.00)	4 (33.30)	1 (10.00)	9 (30.0)	17.911	0.0065*
+1	4 (50.00)	1 (8.30)	1 (10.00)	6 (20.0)		
+2	0	4 (33.30)	1 (10.00)	5 (16.7)		
+3	0	3 (25.00)	7 (70.00)	10 (33.3)		
Total	8 (26.70)	12 (40.00)	10 (33.30)	30		

*Significant difference. IHS: Immunohistochemical score

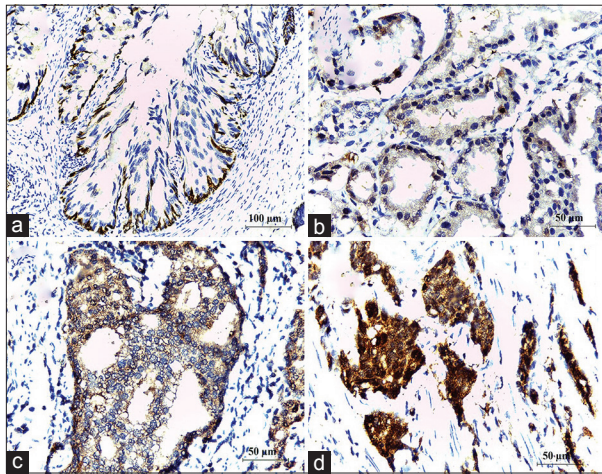


Figure 1: Immunohistochemical expression of maspin in: (a) BPH showing weak (+1) maspin expression restricted to the basal cells (Immunoperoxidase, ×200), (b) well-differentiated prostatic carcinoma showing weak (+1) maspin expression (Immunoperoxidase, ×400), (c) moderately differentiated prostatic carcinoma showing moderate (+2) maspin expression (Immunoperoxidase, ×400), and (d) poorly differentiated prostatic carcinoma showing strong (+3) maspin expression (Immunoperoxidase, ×400)

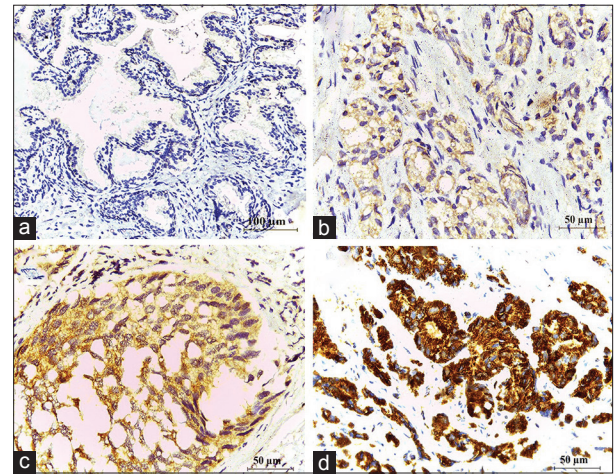


Figure 2: Immunohistochemical expression of prohibitin in: (a) benign prostatic hyperplasia showing negative maspin and prohibitin expression (Immunoperoxidase, ×200), (b) well-differentiated prostatic carcinoma showing weak (+1) maspin and prohibitin expression (Immunoperoxidase, ×400), (c) moderately differentiated prostatic carcinoma showing moderate (+2) maspin and prohibitin expression (Immunoperoxidase, ×400), and (d) poorly differentiated prostatic carcinoma showing strong (+3) maspin and prohibitin expression (Immunoperoxidase, ×400)

understood yet, it is supposed that prostatic carcinoma results from a combination of genetic and environmental factors.^[13,14]

One of the mechanisms associated with prostatic carcinogenesis is mutation of Ras gene and activation of Bcl2. On the other hand, loss of function of tumor suppressor genes also contributes to tumor progression.^[15]

As reported in different organ cancers, maspin and PHB have been suggested to play crucial roles in prostatic carcinogenesis. Maspin is a member of the serine protease inhibitor/noninhibitor superfamily,^[6] which was originally

discovered in normal mammary epithelium.^[15] It was implicated in important processes related to carcinogenesis as suppression of tumor growth and metastasis through inhibition of basement membrane invasion,^[16] enhancement of cell adhesion, and blocking cell migration.^[17] It also has a pro-apoptotic effect through upregulation of bax, especially in human breast and prostatic cancer cells.^[18] Moreover, maspin was claimed to have a potent inhibitory effect on osteolysis occurring in prostate cancer bone metastases.^[19,20] Another important function of maspin is inhibition of angiogenesis^[21]

through blocking fibroblast growth factor and vascular endothelial growth factor-mediated endothelial cell migration. It was also found to inhibit neovascularization in the rat cornea, moreover, maspin-treated prostatic tumor cells showed reduced vascularization in a xenograft mouse model.^[5]

In the current work, maspin showed overexpression by the tumor cells of prostatic carcinoma (70%) of cases, while BPH showed expression only in 20% of cases, was restricted positivity to the basal cells. These results were in accordance with Zou *et al.*,^[5] but contradictory to those reported by Fawzy *et al.*,^[17] who found maspin expression in 93.3% of PBH and 36.6% of prostatic carcinomas. In BPH, they described intense maspin positivity in basal cells with weaker expression in luminal cells. Other studies also reported down-regulation of maspin expression in prostatic carcinomas.^[15,22-26] These conflicting differences may be attributed to the different genetic background of each tumor, the difference in antibodies, immunohistochemical methods, criteria of positive staining, and the methods of statistical analysis used.

The studies that reported downregulation of maspin expression in prostatic carcinomas suggested that the promoter of the maspin gene (CpG) is found in two states, methylation/demethylation. The former is usually associated with overexpression, while the latter is associated with downregulation of maspin. In nontransformed cells, this promoter is usually methylated, while in tumor cells it is hypomethylated. This hypomethylation is suggested to be involved in the cancer development and progression through activation of genes important for carcinogenesis.^[27]

The present study revealed a significant increase in maspin expression with increasing Gleason score in the studied prostatic carcinomas ($P = 0.0125$). This was in accordance with Zou *et al.*,^[5] while contradictory to Fawzy *et al.*^[17] and Machtens *et al.*,^[28] who observed an inverse correlation between maspin expression and the histological grade of their studied prostatic carcinomas.

Actually, as an inhibitor of tumor cell invasion and metastasis, maspin overexpression was expected in better-differentiated tumors; however, the significant positive relationship between maspin expression and Gleason score observed in this study as well as other studies^[5] may be explained by the fact that tumor progression is a complex process involving changes in multiple molecular pathways that interact with each other and is not dependent only on the pathways involving maspin. Another explanation is that the immunohistochemical detection of maspin expression may not predict functional states of maspin, in other words, the presence of maspin protein in tumor cells may represent dysfunctional protein as occurs in the well-known “p53 scenario.” Maspin overexpression detected in poorly differentiated carcinomas may also reflect additional changes acquired by a subset of prostatic tumors that bypass the normal regulation of maspin expression.^[5]

The increased maspin expression in high-grade carcinomas may suggest the association between maspin overexpression

and poor prognosis in prostatic carcinoma patients. This finding is supported by the other studies that reported the association between maspin overexpression and increased aggressiveness of carcinomas in other organs.^[29-31]

Importantly, maspin expression may be a good biomarker for screening of the response of prostatic cancer cells to the androgen ablation therapy. This was reported by Zou *et al.*^[5] who observed upregulation of maspin expression in tumor cells showing histological response to hormonal treatment with neoadjuvant androgen deprivation therapy before surgery in prostatic carcinoma patients. This observation suggests that the androgen withdrawal may unmask maspin expression in prostatic cancer cells which frequently lack its expression.

PHB is another protein that has been observed to show altered expression in prostatic carcinoma. It has been implicated in important cellular processes and found in different cellular compartments including mitochondria, nucleus, and cell membrane. Subsequently, it has different functions according to the subcellular localization.^[32]

Several reports indicated that PHB was generally overexpressed in transformed cells compared to their nontransformed counterparts,^[33] and this forced investigators to find out its role in carcinogenesis. It was considered a tumor suppressor gene based on the findings of different studies. Fusaro *et al.*^[34] and Wang *et al.*^[35] discovered that PHB co-localizes with two important tumor suppressor genes, namely, p53 and Rb. Moreover, it was also discovered to co-localize with the transcription factor E2F, leading to inhibition of its transcriptional activity.^[33] In addition, microinjection of PHB mRNA blocked cell proliferation.^[36]

In addition to its antiproliferative effect, PHB was suggested to have an anti-apoptotic function, as its gene was observed to be downregulated in osteosarcoma cells in response to cytotoxic drugs, while transient overexpression of the PHB coding sequence significantly reduced cytotoxic drug-induced apoptosis in these cells.^[37]

It was suggested that PHB may play a role in the cellular growth response to androgen stimulation in prostatic cancer cells.^[38] It was found to be downregulated in androgen-stimulated proliferating prostatic cancer cells. Cell-cycle analysis of prostatic cancer cells showing reduced levels of PHB revealed high percentage of cycling cells, whereas cells with increased PHB levels showed lower percentage entering the cell cycle, suggesting that the regulation of PHB is a crucial part of the cellular growth response to androgens.^[39]

In the current work, high PHB expression was observed in prostatic carcinoma cases (70% of cases), while all BPH cases showed negative expression. This was in agreement with Ummanni *et al.*,^[40] who reported that PHB was highly expressed in prostatic intraepithelial neoplasia and prostatic carcinoma, but not in benign prostatic epithelium or proliferative inflammatory atrophy, suggesting that PHB expression may occur early in the development of cancer, and

its expression may be useful to distinguish between prostatic carcinoma and BPH.

The present study further revealed a highly significant positive association between PHB expression and Gleason score ($P = 0.0065$), as it showed higher expression with increasing Gleason score. Such relation was not investigated, to the best of our knowledge, by previous studies, and it suggests that PHB overexpression may be associated with poor prognosis in prostatic carcinoma. This finding was supported by other studies that showed association between upregulation of PHB expression and poor prognosis in other cancers as bladder carcinoma.^[41]

As discussed in association with maspin, the tumor suppressor actions of PHB entails its downregulation in cancers rather than overexpression. However, the current study, as well as other studies,^[8] reported its upregulation in different organ cancers. Different explanations were suggested for PHB overexpression in proliferating cells, one of them is the presence of regulatory elements in the PHB promoter that bind to the Myc oncoprotein,^[42] which is commonly upregulated in proliferating cells, and its upregulation induces the expression of PHB.^[43] Other explanations include the mutation of PHB gene,^[44] its upregulation as a result of metabolic stress after heat shock or oxidative stress, or as one of the attempts of the cell to suppress the high proliferation rate.^[8]

CONCLUSIONS

Overexpression of maspin and PHB in prostatic carcinoma reflects their vital roles in prostatic carcinogenesis. Their upregulation with increasing Gleason score indicates their prognostic significance. Moreover, PHB may differentiate between prostatic carcinoma and BPH being expressed only by malignant cells.

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Conflicts of interest

There are no conflicts of interest.

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