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Original article

The Significance of Expression of MUC 4 and IMP-3 in Benign Prostatic Hyperplasia, High Grade Prostatic Intraepithelial Neoplasia and Prostatic Adenocarcinoma (immunohistochemical study)

Zeinab I. Elshawarby [a], Kareem A. El Attar [b], Naglaa H. Shalan [a]

[a] Pathology Department, Faculty of Medicine Benha University, Egypt.

[b] Urology Department, Faculty of Medicine Benha University, Egypt.

Corresponding to:
Dr. Naglaa H. Shalan.
Pathology Department, Faculty of Medicine Benha University, Egypt.

Email:
drnaglaahamed@yahoo.com

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Abstract:

Background: Prostate cancer is one of the most frequent malignancies worldwide. Mucin 4(MUC4) is a transmembrane mucin that is contributed in cell signaling events that guide the proliferation of cells. Insulin-like growth factor 2 (IGF2) messenger RNA binding protein 3 (IMP3) has been linked to tumorgenesis and progression of many cancers. **Aim:** This study aimed to evaluate MUC4 and IMP-3 expression in different prostatic lesions and to relate the results with clinicopathological data. **Material and method:** This retrospective study examined 40 cases including 10 cases of benign prostatic hyperplasia (BPH), 6 cases of high-grade prostatic intraepithelial neoplasia (HGPIN) and 24 cases of prostatic adenocarcinoma (PCa) . MUC 4 and IMP-3 were used for immunohistochemistry. **Results:** MUC4 was detected in (100%) of BPH & HGPIN cases and (16.6%) of prostatic carcinoma. IMP3 expressed in (100%) of prostatic cancer cases and expressed in(10%) &(16.7%) of &HGPIN respectively. A significant statistical correlation between IMP3expression and stage, Gleason's grade, pre OP serum PSA level>10ng/ml, capsular and perineural invasion(P<.001). **Conclusion:** MUC4 down regulation may be important in identifying the molecular underpinnings of PC. Association between IMP3 over expression and poor prognosis suggesting that PC patients may benefit from a targeted anti-IMP3 therapy.

Keywords: MUC4, IMP3.BPH, Prostatic adenocarcinoma.

Introduction

Prostatic carcinoma is the most common male malignancy and a leading cause of death, with dietary and hereditary risk factors including germline DNA repair mutations [(1).]

The exact etiology of prostate cancer is still elusive. Variable modifiable and unmodifiable factors are thought to be contributing factors such as genetic predisposition, diet, infections, hormonal imbalance, and exposure to toxins[(2)].

High incidence of prostate cancer can also be due to increasing use of prostate specific antigen (PSA) screening and better methods of diagnosis. Studying the etiology, pathophysiology, and natural history of prostate cancer can be helpful to reach the proper diagnosis and provide a better management of this cancer [(3).]

Mucins are glycoproteins that have a role in the protection and lubrication of epithelial surfaces and contributed in signal transduction pathways that regulate the process of morphogenesis [(4).] Mucins have the ability to control a number of cellular processes such as growth, differentiation, transformation, invasion, adhesion and immune surveillance. However, the mucin molecule itself becomes changed during progression in cancer cells [(5)].

Studies have revealed that MUC4 is a transmembrane mucin and epithelial cells in variable tissues expressed it. Normally, luminal epithelial cells of the stomach, colon, lung, trachea, cervix, and prostate- expressed MUC4[(6)].

Insulin-like growth factor 2 (IGF2) messenger RNA binding protein 3 (IMP3)- has been identified as an oncofetal protein, which is over expressed and predicts a poor prognosis in several kinds of human cancers, such as breast cancer, cervical cancer, colon cancer and bladder cancer. It is one of the three members of IGF2BP family which modulates the transport and translation of mRNA through binding to the coding regions of target mRNAs, such as IGF2, MYC, and β-actin. The functions and mechanisms of IMP3 in prostate cancer progression still remain largely unknown [(7)].

In the current study, we aimed to reveal the role of IMP3 in pathogenesis or prognosis of prostatic cancer.

Material and Methods:

This retrospective study was done on 40 cases of different prostatic lesions as follows: 10 of them were diagnosed BPH, 6 were HGPIN and 24 were prostatic adenocarcinoma. Cases were obtained from Pathology Department and Early Cancer Detection Unit; Benha Faculty of Medicine, through the years 2015 -2019. The study was approved by the Ethical committee of faculty of Medicine, Benha University (Rc.27.2.2023).

Different clinicopathological information, such as the patient's age, pre-operative PSA serum level, depth of tumor invasion p(T), lymph node metastasis, and distant metastasis- were obtained from the patients' files. Sections were prepared from paraffin blocks, Hematoxylin and Eosin sections were reviewed by two pathologists to confirm diagnosis.

Prostatic adenocarcinoma cases were classified according to the WHO classification [(8).] The Gleason scoring system was used to grade prostatic adenocarcinoma patients, and it was based on the recommendations of the 2014 International Society of Urological Pathology (ISUP) consensus conference [(9).] The prostatic adenocarcinoma cases were classified into Grade Group I (Gleason score 3 + 3), Grade Group II (3 + 4), Grade Group III (4 + 3), Grade Group IV (4 + 4, 3 + 5, or 5 + 3), and Grade Group V (4 + 5, 5 + 4, or 5 + 5)- based on the latest Gleason Grade Group (GGG) classification. For PCa cases, TNM staging was carried out in accordance with the AJCC staging system [(10).]

Immunohistochemical study:

On positive charge slides, three 4-mm thick formalin-fixed, paraffin-embedded tissue sections- were prepared. Streptavidin-biotin method is used for immunohistochemical analysis in accordance with the manufacturer's recommendations. Antibodies are shown in (Table 1).

For the secondary developing reagents, we used a standard labeled streptavidin-biotin system *(Dako-Cytomation, Denmark, A/S)*. Diaminobenzidine solution diluted to 0.02% was used as chromogen. Hematoxylin was then used as a counterstain. For each marker, the primary antibody stage was skipped, and the normal rabbit serum IgG in its place was utilized as a negative control.

Positive control

Normal bronchial epithelium was used as a positive control for MUC4, Aborted fetal liver (16 weeks) was used as a positive control for IMP3.

MUC4 interpretation:

MUC4 was detected as cytoplasmic and or membranous brown coloration. Immunoreactivity index was evaluated according to the extent and intensity of stained cells as reported by Rokutan-Kurata M et al [(11)] and Mawas AS et al [(12)].

IMP3 interpretation:

IMP3 was detected as cytoplasmic or membranous brownish coloration. Immunoreactivity was evaluated according to intensity and proportion, as reported by Madkour, S et al [(13)].

Statistical analysis: The collected data was recorded then presented, and statistically analyzed by computer using Statistical Package for the Social Sciences (SPSS) 25.0 for windows (SPSS Inc., Chicago, IL, USA).

Categorical data were expressed as numbers and percentages. Numerical data were expressed as mean ± standard deviation. Pearson Chi square test (X2) was used to assess relations between groups. P-value >0.05 was considered non-significant (NS), <0.05 significant (S), ≤ 0.01 highly significant (HS).

Table (1): Antibodies used in the study.

Antibody	Source	dilution	Incubation period	Staining pattern
MUC4	***Chongqing, 400039, China***	1:50	Overnight at room temperature	Cytoplasmic and or membranous
IMP3	***Chongqing, 400039, China***	1:100	Overnight at room temperature	Cytoplasmic

Results

Clinico-pathological results:

The examined 24 cases of prostatic adenocarcinoma including:7 cases (29.2%) of Gleason grade I, 3 cases (12.5%) of grade II, 5 cases (20.8%) of grade III, 6 cases (25%) of grade IV and 3 cases (12.5%) of Gleason grade V. Regarding the stage ,only one case (4.5%) of stage I,10(41.7%) cases of stage II ,8(33.3%) cases of stage III,5 (20.8%) cases of stage IV. On evaluation of lympho-vascular invasion, negative cases were 22 (91.7%) and positive cases were 2 (8.3%). Regarding perineural invasion, positive cases were 12 (50%) and negative cases were 12 (50%).

Immunohistochemical results:

Immunohistochemical results of MUC4 expression. Positive MUC4 expression was detected as brownish cytoplasmic staining in all cases (100%) of benign prostatic hyperplastic (BPH); of which 7cases (70%) showed moderate, 2 cases (20%) showed strong, and 1case (10%) showed weak expression. Also, all PIN cases (100%) showed positive

expression in which ,4 cases (66.7%) showed moderate ,1 cases (16.7%) showed strong, and 1case (16.7%) showed weak expression. In contrast, of the total 24 malignant tumor tissue samples, 20(83%) showed negative expression and only 4(16.6%) cases were positive with 2(8.3%.) cases with weak and 2(8.3%) cases with moderate expression. There was a highly significant statistical associations between MUC4 expression and studied group (P<.001) (Table 2) (figure 1).

Table (2): Expression of MUC4 and IMP3 marker in the studied group.

Marker	Type of lesion	Cancer (N=24)	BPH (N=10)	PIN (N=6)	Chi-square test	P value
MUC4	Negative	20	0	0	29.01	<.001(HS)
	(N=20)	83.3%	0.0%	0.0%		
	Weak (+1)	2	1	1		
	(N=4)	8.3%	10 %	16.7%		
	Moderate (+2)	2	7	4		
	(N=13)	8.3%	70.0%	66.7%		
	Strong (+3)	0	2	1		
	(N=3)	0.0%	20.0%	16.7%		
IMP3	Negative	0	9	5	33.88	<.001(HS)
	(N=14)	0.0%	90.0%	83.3%		
	weak	6	1	1		
	(N=8)	25.0%	10.0%	16.7%		
	Moderate	14	0	0		
	(N=14)	58.3%	0.0%	0.0%		
	Strong	4	0	0		
	(N=4)	16.7%	0.0%	0.0%		

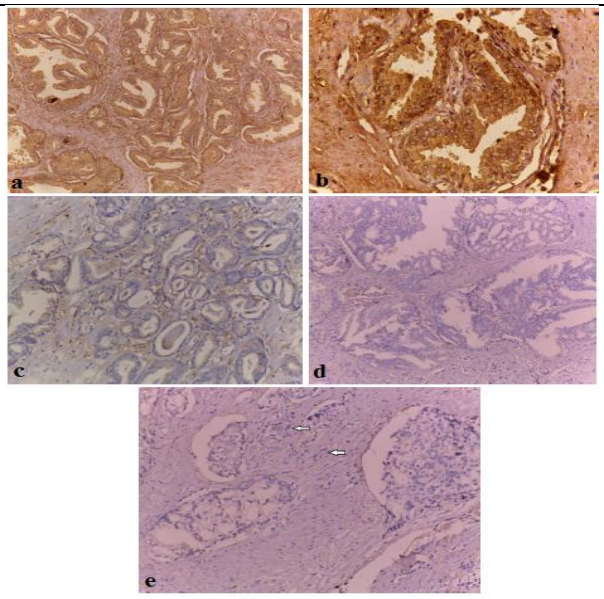

Figure (1): Shows MUC4 expression. Figure (1.a): A case of Benign prostatic hyperplasia showing moderate positive MUC4 expression (IHC, ABC x100). Figure (1.b): A case of high grade prostatic intraepithelial neoplasia showing strong positive MUC4 expression (IHC, ABC x400). Figure (1.c): A case of prostatic adenocarcinoma Gleason Grade Group (II) show negativeMUC4 cytoplasmic expression (IHC, ABC x200). Figure (1.d): A case of prostatic adenocarcinoma Cribriform pattern (Gleason Grade Group IV) showing Negative MUC4 cytoplasmic expression (IHC, ABC x100). Figure (1.e): A case of prostatic adenocarcinoma (Gleason Grade Group V) showing negative MUC4 cytoplasmic expression ,scattered sheets of malignant cells showed negative expression (IHC, ABC x200).

A significant statistical correlation was detected between MUC4 expression and PSA serum level (P.027). However, there was no correlation with other parameters (Table 3).

Immunohistochemical results of IMP3 expression. Positive IMP3 expression was determined as a brownish cytoplasmic staining in all cases (100%) of prostatic adenocarcinoma, of which 14(58.3%) showed moderate, 4 cases (16.7%) showed strong, and 6case (25%) showed weak expression. In contrast, of the total 10 cases of BPH ,9 (90%) showed negative expression and only one (10%) showed weak expression. Also 5(83%) of PIN cases showed negative expression and only one cases (16.7%) showed weak expression. The difference of IMP3 immunoreactivity between study groups was highly significant ($p < 0.001$) (Table2) (figure2).

A highly significant statistical association was detected between IMP3 expression and the stage, strong expression was detected in 80% of stage IV (P= 0.002). Also, there was a highly significant statistical association between IMP3 expression and the Gleason's grade. Strong expression was detected in 100% of grade 5(P= 0.003). Also, there was a highly significant statistical association between IMP3expression and the preoperative serum PSA level. Strong expression was detected in 66.7% of cases with PSA >10ng/ml (P= 0.001). A highly significant statistical association was detected between IMP3expression and capsular and perineural invasion (P= 0.006) (Table 4).

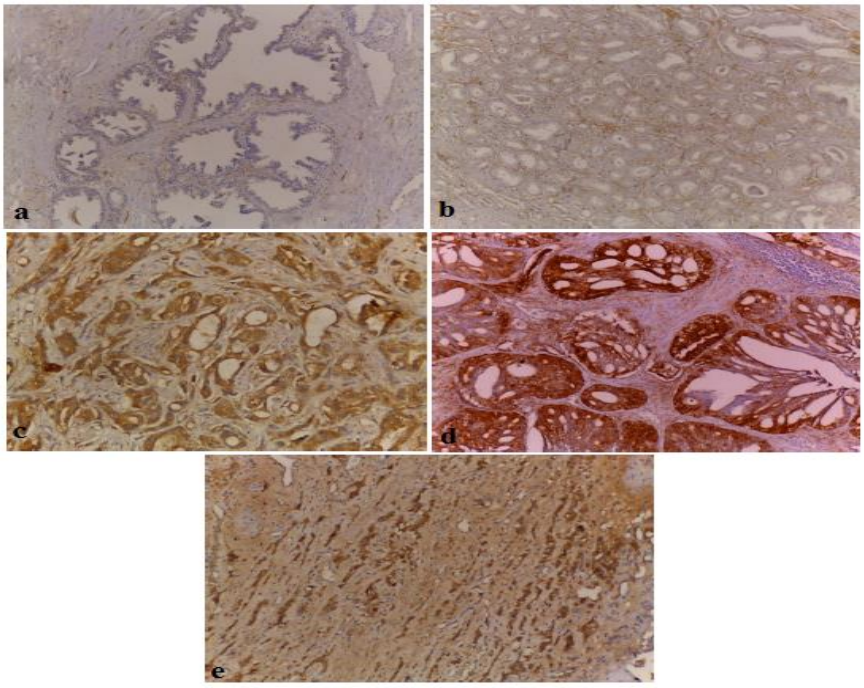

Figure (2): Shows IMP3 cytoplasmic expression. Figure (2.a): A case of Benign prostatic hyperplasia showing negative IMP3 cytoplasmic expression (IHC, ABC x100). Figure (2.b): A case of prostatic adenocarcinoma Gleason Grade Group I show weak positive IMP3 cytoplasmic expression (IHC, ABC x100). Figure (2.c): A case of prostatic adenocarcinoma Gleason Grade Group (II) show moderate positive IMP3 cytoplasmic expression (IHC, ABC x400). Figure (2.d): A case of prostatic adenocarcinoma Cribriform pattern (Gleason Grade Group IV) showing strong positive IMP3 cytoplasmic expression (IHC, ABC x100). Figure (2.e): A case of Prostatic adenocarcinoma Gleason Grade Group V showing cords of malignant cells with moderate to strong positive IMP3 cytoplasmic expression (IHC, ABC x100).

Table (3): Relation between MUC4 expression and clinicopathological parameters of studied cases.

Marker		**MUC4**				**Chi-square test**	**P value**
Variable		Negative (N=20)	weak (N=4)	Moderate (N=13)	Strong (N=3)		
Age groups	**<65 (21)**	11 52.4%	1 4.8%	7 33.3%	2 9.5%	1.514	.679
	>65 (19)	9 47.4%	3 15.8%	6 31.6%	1 5.3%		
T	**T2 (10)**	7 70.0%	1 10%	2 20%	0 0.0%	3.22	.20
	T3 (14)	13 92.9%	1 7.1%	0 0.0%	0 0.0%		
N	**Present (5)**	4 80%	1 20%	0 0.0%	0 0.0%	1.56	.457
	Absent (19)	16 84.2%	1 5.3%	2 10.5%	0 0.0%		
Stage	**First (1)**	1 100.0%	0 0.0%	0 0.0%	0 0.0%	4.920	.554
	Second (10)	7 70.0%	1 10.0%	2 20.0%	0 0.0%		
	Third (8)	7 87.5%	1 12.5%	0 0.0%	0 0.0%		
	Forth (5)	5 100.0%	0 0.0%	0 0.0%	0 0.0%		
Grade	**1 (7)**	6 85.7%	0 0.0%	1 14.3%	0 0.0%	9.326	.316
	2 (3)	1 33.3%	1 33.3%	1 33.3%	0 0.0%		
	3 (5)	4 80.0%	1 20.0%	0 0.0%	0 0.0%		
	4 (6)	6 100.0%	0 0.0%	0 0.0%	0 0.0%		
	5 (3)	3 100.0%	0 0.0%	0 0.0%	0 0.0%		
PSA group	**<4ng/ml (15)**	2 13.3%	2 13.3%	9 60.0%	2 13.3%	15.92	.014 (S)
	4-10ng/ml (19)	12 63.2%	2 10.5%	4 21.1%	1 5.3%		
	>10ng/ml (6)	6 100%	0 0.0%	0 0.0%	0 0.0%		
Capsular	**Present (12)**	11 91.7%	1 8.3%	0 0.0%	0 0.0%	2.20	.33
	Absent (12)	9 75.0%	1 8.3%	2 16.7%	0 0.0%		
Lymph vascular	**Present (2)**	2 100.0%	0 0.0%	0 0.0%	0 0.0%	.436	.804
	Absent (22)	18 81.8%	2 9.1%	2 9.1%	0 0.0%		
Perineural	**Present (12)**	10 83.3%	2 16.7%	0 0.0%	0 0.0%	4.00	.135
	Absent (12)	10 83.3%	0 0.0%	2 16.7%	0 0.0%		

Table (4): Relation between IMP3expression and clinicopathological parameters of studied cases.

Variable	Marker	IMP3 Negative (N=14)	Weak (N=8)	Moderate (N=14)	Strong (N=4)	Chi-square test	P value
Age groups	**<65 (21)**	8 38.1%	5 23.8%	6 28.6%	2 9.5%	.974	.808
	>65 (19)	6 31.6%	3 15.8%	8 42.1%	2 10.5%		
T	**T2 (10)**	0 0.0%	3 30.0%	7 70.0%	0 0.0%	3.429	.180
	T3 (14)	0 0.0%	3 21.4%	7 50.0%	4 28.6%		
N	**Present (5)**	0 0.0%	0 0.0%	3 60.0%	2 40.0%	3.645	.162
	Absent (19)	0 0.0%	6 31.6%	11 57.9%	2 10.5%		
Stage	**First (1)**	0 0.0%	1 100.0%	0 0.0%	0 0.0%	21.25	.002(HS)
	Second (10)	0 0.0%	3 30.0%	7 70.0%	0 0.0%		
	Third (8)	0 0.0%	2 25.0%	6 75.0%	0 0.0%		
	Forth (5)	0 0.0%	0 0.0%	1 20.0%	4 80.0%		
Grade	**1 (7)**	0 0.0%	4 57.1%	3 42.9%	0 0.0%	23.39	.003 (HS)
	2 (3)	0 0.0%	1 33.3%	2 66.7%	0 0.0%		
	3 (5)	0 0.0%	1 20.0%	4 80.0%	0 0.0%		
	4 (6)	0 0.0%	0 0.0%	5 83.3%	1 16.7%		
	5 (3)	0 0.0%	0 0.0%	0 0.0%	3 100 %		
PSA group	**<4ng/ml (15)**	10 66.7%	2 13.3%	3 20.0%	0 0.0%	34.72	.001 (HS)
	4-10ng/ml (19)	4 21.1%	6 31.6%	9 47.4%	0 0.0%		
	>10ng/ml (6)	0 0.0%	0 0.0%	2 33.3%	4 66.7%		
Capsular	**Present (12)**	0 0.0%	0 0.0%	8 66.7%	4 33.3%	10.28	.006 (HS)
	Absent (12)	0 0.0%	6 50.0%	6 50.0%	0 0.0%		
Lymph vascular	**Present (2)**	0 0.0%	1 50.0%	0 0.0%	1 50.0%	3.273	.195
	Absent (22)	0 0.0%	5 22.7%	14 63.6%	3 13.6%		
perineural	**Present (12)**	0 0.0%	0 1.	8 66.7%	4 33.3%	10.28	.006 (HS)
	Absent (12)	0 0.0%	6 50.0%	6 50.0%	0 0.0%		

Discussion

Prostate cancer (PCa) is considered the second most common cancer in men globally with 1.4 million new cases identified each year, and one of the leading causes of cancer-related death in males, accounting for 350,000 fatalities each year globally **(14).**

Prostate cancer (PCa) has an aggressive metastatic nature and silent coarse, so early diagnosis and treatment is difficult. **(15).** However, PCa with advanced course usually progresses to lethal PCa, which is considered incurable progresses despite androgen ablation and develops also castration resistance **(16)**. So, there is an urgent need for more effective and lasting treatment for PCa.

MUC4 is one member of the mucin family that have a significant role in tumor growth, intracellular and extracellular signaling, tumor-stromal interactions, metastasis, immunity- and chemotherapeutic agent-resistance **(5).**

The current study determined MUC4 expression in BPH, PIN and prostatic adenocarcinoma. There was a significant down regulation of MUC4 expression in prostatic adenocarcinoma when compared to the other groups. These results were in agreement with previous studies (5.,17.,18). A study by Singh et al., (17) showed that there was enhancement of MUC4 expression after adding histone deacetylase inhibitors and DNA methyl transferase inhibitors with prostate cancer cell lines.

The prostate cancer etiology may be regulated by an epigenetic process that controls MUC4 expression. Additionally, areas of PIN showed positivity, showing that the loss of MUC 4 expression happens when the lesions advance(17).Similar to the current study ,a study by Kaur et al.,(19) showed intense MUC4 expression in normal epithelium and its progressive loss in advanced carcinoma stage followed by its complete loss in high and low grade invasive urinary bladder carcinoma .Contrary to the current study, studies by Andrianifahanana et al.,(20), and Gautam et al.,(21) observed MUC4 expression is exclusively associated with Pancreatic carcinoma and is absent in the normal pancreas. Also, a study by Senapati et al., (22) showed that there was over expression of MUC4 in gastric cancer tissues than adjacent normal tissues and also found that MUC4 over expression was linked to the aggressive phenotype of gastric cancer cells and associated with increasing activation of ErbB2 oncoprotein. Another study by Elsayed et al., (23) revealed MUC4 over expression in lung adenocarcinoma associated with aggressive behavior.

According to **(24)** the reason for such inconsistent results in MUC4 correlations with many variables is that MUC4 might be a mediator or indication of tumor growth and aggressiveness. MUC4 binds to ErbB2 and phosphorylates it on its tyrosine residues. There are two mechanisms by which MUC4 phosphorylates ErbB2 on its tyrosine residues, and the prognostic value of MUC4 is dependent on which of the two pathways is active.

The current study showed that MUC4 was down regulated in the majority of prostatic carcinoma which came in contrast to other known malignancies and that may be due to the small number of cases in this study. Understanding the mechanism of MUC4 downregulation in prostate cancer and clarification of its precise function need investigation with bigger samples.

The oncofetal protein IMP3 modulates, the translational regulation of Insulin-like Growth Factor II leader-3 mRNA during cell proliferation and in cell adhesion**(25)** ,and regulates CD166 and CD24, each of which previously known as prognostic indicator for prostate cancer**(26-27)**.We therefore anticipated that IMP3 would have a predictive significance in prostate cancer and it has been detected in other malignancies with the same result

(28-31) which came in line with our current study.

Additionally, in non-small cell lung cancer with the use of an anti-IMP3 immunotherapy demonstrated a good level of safety and may present a challenged treatment alternative to several different cancers.**(32-33)**.This shows that IMP3 is not only a very promising target for therapy but also has a high diagnostic potential, indicating that more research into this member of the insulin-like growth factor II mRNA binding protein family, is necessary.

The current study showed that IMP3 expression was present in all cases of prostatic cancer but only rarely expressed in BPH &PIN. This was in agreement with Ikenberg et al., [34] and Szarvas et al., [35] who observed IMP3 expression in prostatic cancer and no expression in BPH cases. Consistently a study by Zhang et al., [36] found significant increases in the mRNA and protein levels of IMP3 in prostate cancer tissues and cell lines as compared with normal tissues and cells. In contrast to our results, a study by Yildirim and Sentürk [37] found no IMP3 expression in BPH, PIN, Prostatic cancer. Also, a study by Burdelski et al., [31] who investigate IMP3 expression in human cancers especially the epidemiology and clinical relevance of with employment the approach of a two-step tissue microarrays (TMAs). They observed no IMP3 expression in normal or tumorous tissues. This disparity may be due to the use of different clones of antibodies, different means of interpretation, different technique and different sample size.

Significant statistical associations were found between the stage and IMP3 expression. Similarly, according to a study by Szarvas et al., [35], IMP3 was shown to be positively expressed in 15% of tissues from clinically localized prostate cancer and in 65% of tissues from metastatic prostate that had undergone palliative care.

There was a significant statistical association between IMP3 expression, Gleason's grade and preoperative PSA serum level. The strong expression was in higher grade & higher pre-operative PSA level. Similar study by Ikenberg et al., [34] who observed IMP3 expression with higher rates were observed in cases with higher Gleason scores and higher preoperative PSA level. Similarly [35] observed significant statistical associations between IMP3 expression and Gleason's grade. However, no correlation between IMP3 immunostaining and pre-operative PSA level.

There was statistically significant association between IMP3 &capsular, perineural invasion. Similarly, a study by Chromecki et al., [38] found statistically significant correlation between IMP3 andperineural invasion in prostatic carcinoma. Also, study by Damasceno et al [39] found statistically significant correlation between IMP3&perineural invasion in gastric cancer.

Insulin growth factor (IGF) signaling is known to be activated by IMP3, which also increases cell growth, proliferation, and radiation resistance [40]. By inhibiting miRNA binding, it has been demonstrated to enhance the expression of HMGA2 (high mobility group AT-hook 2), resulting in proliferation and migration. It plays a role in enhancing the expression of cyclins by providing synergistic interaction with heterogeneous nuclear ribonucleoprotein M (HNRNPM) in the nucleus [41]. According to study by Zhang et al., [36] revealed that IMP3 accelerates the progression of prostate cancer via activating PI3K/AKT/mTOR pathway through increasing SMURF1-mediated PTEN ubiquitination.

In the process of prostate cancer metastasis, there was activation of ERK signaling pathway and triggering epithelial-mesenchymal transition (EMT) programming, and this ultimately accelerating metastasis which occurred by physical binding of IGF2BP3 to circular RNAhsa_circ_0003258 in the cytoplasm to enhance HDAC4 mRNA stability **(42)**.

Conclusion:

MUC4 down regulation may be important in identifying the molecular underpinnings of PC. Association between IMP3 over expression and poor prognosis suggesting that PC patients may benefit from a targeted anti-IMP3 therapy.

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