Original Research Article

Immunohistochemical loss of expression of estrogen receptor beta as a significant diagnostic marker in prostatic carcinoma

M.Dina Mary[1], Shantaraman Kalyanaraman[2*], Deepadevi .G[3], Vasuki Muthuraman[4]

[1]Assistant Professor, Department of Pathology, Tirunelveli Medical College, Tirunelveli, Tamil Nadu, India
[2]Professor, Department of Pathology, Tirunelveli Medical College, Tirunelveli, Tamil Nadu, India
[3]Tutor, Department of Pathology, Tirunelveli Medical College, Tirunelveli, Tamil Nadu, India
[4]Associate Professor, Department of Pathology, Tirunelveli Medical College, Tirunelveli, Tamil Nadu, India

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Abstract

Background: Prostate is the site of two of the most common diseases in elderly men, BPH and Prostatic adenocarcinoma(PCa). Androgen dependency of prostate has long been known. But, role of estrogen in prostate and human prostate carcinogenesis has only been recently recognized. Estrogen receptor(ER) has opposing effects in prostate via two isoforms ER α and β. Current studies suggest that decreased expression of ERβ is associated with PCa, while ERα is oncogenic. But, some studies in literature showed that ERβ2 and ERβ5 promote invasion and metastasis in PCa.This study was done to evaluate and correlate the patterns of immunohistochemical expression of ERα and ERβ in patients with PCa, prostatic intraepithelial neoplasia (PIN) and BPH. **Materials and methods:** This study includes 69 cases of prostatic lesions, including 23 PCa and 46 BPH cases. We have done IHC with 4 markers including, p63, AMACR, ERα and ERβ in sections from formalin fixed paraffin blocks of tissues from all 69 cases. **Results:** IHC expression of p63, AMACR and ERβ showed statistically significant difference between PCa and BPH cases, at p value <0.005. All PCa cases showed p63-ve and AMACR +ve immunostaining and vice versa was true in all BPH cases. PCa cases showed lower ERβ expression in both epithelial and stromal compartments compared to BPH cases. No significant difference in expression of ERα between PCa and BPH cases. **Conclusion:** ERβ may have an antiproliferative role in prostate carcinogenesis and may be targeted for newer therapeutic options.

Keywords: Estrogen receptor, ERα, ERβ, prostate, immunohistochemistry

Introduction

Prostate is the site of two of the most common diseases in elderly men, BPH and Prostate adenocarcinoma[1]. Both are disorders of cell differentiation and proliferation1. Prostatic carcinoma is the 2nd most common cancer and 6th leading amond causes of death due to cancer in males world-wide[1,2] Prostatic carcinoma is extremely rare before 40 years but incidence increases with age at approximately 10th power of age[3]. The major limitation in management of prostatic carcinoma is control of tumor growth and prevention of metastasis.

Prostate gland has 2 phenotypes of epithelial cells -luminal and basal cells separated by basement membrane from stroma1. Exact etiology of BPH is still not fully elucidated. However it is known that complex epithelial - stromal interactions along with hormonal factors are responsible for BPH development[4]. Nuclear hormone receptors including androgen receptors, progesterone receptors and estrogen receptors have been reported to be important modulators of prostate growth and differentiation[5]. ER has both genonmic and nongenomic functions including membrane signaling leading to post translational modification of many proteins[5].

Prostate expresses two ER subtypes –ERα and ERβ encoded by 2 separate genes ESR1 and ESR2[5]. ERα was initially thought to mediate all estrogenic actions. In 1996, ERβ was identified and found to differ significantly from ERα which arose new interest in the treatment of prostatic carcinoma. ERα is predominantly expressed in female reproductive organs while ERβ is highly expressed in male reproductive tract including prostate[6].

*Correspondence
Dr. Shantaraman Kalyanaraman
Professor, Department of Pathology, Tirunelveli Medical College, Tirunelveli, Tamil Nadu, India
E-mail: shantaraman_kal@tvmc.ac.in

Estrogenic action in prostate is mediated by specific intracellular estrogen receptors, activation of which can occur independent of serum estrogen levels[5]. In prostate, ERα is predominantly present in stromal cells, ERβ in basal epithelia[3,4]. Structurally ERβ is highly homologous to ERα in the DNA binding domain (95% AA identity) but exhibit only 60% homology in ligand binding domain[7,8,9]. Many studies have demonstrated increased ER expression and differential expression of subtypes in BPH specimens as well as in cell cultures[5]. ER has stimulatory as well as inhibitory effect on cell proliferation in prostate via activation of two separate isoforms ER α (proliferative) and β (antiproliferative) respectively[2,5,10].

Current studies suggest that ERα is oncogenic mediating harmful effects while decreased expression of ERβ is associated with prostatic carcinoma. ERβ is fully expressed in BPH[11]. Expression of ERα was found to result in shorter progression free survival and increased risk of developing castration-resistant prostate cancer (CRPC)[12]. These observations support the hypothesis that ERα can act as an oncogene and ERβ has tumour suppressive functions.

Declining levels of ERβ has been observed in benign prostatic hyperplasia progressing to prostatic carcinoma[13], with a further decrease as the Gleason grade of prostate cancer increases[14]. ERβ expression is low in high-grade prostatic intraepithelial neoplasia(HGPIN) of the prostate[15], (reflecting its pre-malignant phenotype and its expression declines with development of prostate cancer, resulting in epithelial dedifferentiation and growth of high-grade, aggressive tumours[16].

Estrogen-related pathways are important in the development and progression of prostate cancer, but the role of ERα and ERβ have numerous contradictions in the present body of literature. Our current understanding ofER biology of the prostate is inadequate to aid precise manipulation of the molecular machinery[17].

To determine whether ERβ represents a useful therapeutic target in prostate cancer, and more specifically in CRPC, it is important to

validate these mechanisms given, that ERα and ERβ can homodimerise or heterodimerise with each other, the issue of cross-reactivity between different estrogenic ligands, the variation in effects of ERβ isoforms and the contradictory finding that ERα and ERβ recognise the same DNA-binding sites[18].

Prostatic adenocarcinoma is a slow progressive disease which can metastazise to the bones and usually presents with debilitating fractures. With an increasing and rapidly graying population in India, the incidence of Prostatic Adenocarcinoma is bound to increase. Hence the risk of mortality of cancer is compounded by an increase in risk of significant morbidity. Targeted therapy that can act on the primary as well as the secondary sites well is required, which is presently lacking. Anti androgenic treatment like castration and estrogen therapy has give limited results. The appearance of the castrate resistant prostate cancer (CRPC) is hence a indication for search for better targets at treatment. The limited success of the estrogen treatment has made greater search in this direction necessary. The identification of ER subtypes ERα and ERβ and further on the ER β isoforms has thrown some light. But the existing literature has numerous contradictions in our understanding of ER biology of the prostate and is inadequate to aid drug development.

Aims and objectives

To describe and correlate the patterns of immune histochemical expression of ERα and ERβ in patients with various grades of Prostatic Carcinoma, various grades of prostatic intra epithelial neoplasia and benign prostatic hyperplasia.

Materials and methods

Present study is a bidirectional, descriptive study, to evaluate and correlate the immunohistochemical patterns of ERα and ERβ in prostatic lesions. This study was carried out in ICMR,Tirunelveli medical college over a period of 3 years, from 2017 to 2020 . The study material includes 69 cases of prostatic lesions (benign and malignant) diagnosed in TURP specimens or prostatic needle biopsies. Formalin fixed paraffin blocks and histopathology slides stained with routine hematoxylin and eosin (H & E) staining, of prostatic lesions from 2013 to 2019 were collected.

Inclusion criteria

Prostatectomy, TURP and needle biopsies specimens

Exclusion criteria

1. Samples of patients on hormone therapy and / with co-morbidities such as stroke, neurogenic bladder, leading to lower urinary tract symptoms
2. Inadequate biopsy tissue samples
3. Autolysed specimens

Instituitional Ethical Committee approval was obtained.Clinical details including patient details, clinical history, DRE findings, Serum PSA levels and other relevant investigations if done, were recorded from case sheets of patients. Paraffin blocks of representative bits of all prostate specimens received at department of pathology during the study period were collected. One section from each block was processed with H&E staining and a primary diagnosis was made, based on WHO classification. Sections diagnosed as BPH, PIN, and PCA were processed for IHC. PIN cases were classified as low grade [LG] and high grade [HG] and PCA cases classified as well differentiated [WD] , moderatetly differentiated [MD] and poorly differentiated [PD] with Gleason score upto 5, 6&7 and 8 to 10 respectively6.Two Sections from each block were processed for IHC with P63(Dako, mouse monoclonal Ab, IR662) and AMACR (Pathinsitu, rabbit monoclonal Ab, 13H4)for a confirmatory diagnosis.2 sections from each block were then processed for IHC with ER α(Immunotag, mouse monoclonal Ab, P03372) and ERβ (Immunotag, mouse monoclonal Ab, PT0318).

Interpretation of p63 immunostaining

Positive staining was taken as proof of benignity and negative staining of the suspicious focus was taken as presumptive evidence of malignancy.

Interpretation of AMACR immunostaining

AMACR staining is used to confirm malignant diagnosis. The staining was considered positive if the staining was circumferential, dark diffuse or granular, cytoplasmic or luminal. The staining is considered negative if there is no staining or if it is focal, faint and noncircumferential[14].

Interpretation of ERα and ERβ immunostaining

As ERα and ERβ are nuclear localized steroid receptors, positive nuclear immunostaining was scored. Nuclear staining, whether weak or strong, was considered positive. ≥200cells were counted separately in epithelial (basal and secretory) compartment and in stroma and percentage calculated. The result was considered as positive, if ≥5% of cell nuclei were immunoreactive. IHC scores were expressed as 0, 1, 2, 3 and 4, with corresponding percentage of cells showing nuclear immunoreactivity to be 0%, 1-4%, 5-10%, 11-20% and>20% respectively[6]. In stroma, only the nuclear stained fibroblasts and myofibroblasts were considered.

Observation and results

This study had a total of 69 cases, which included 64 TURP specimens and 5 prostatic needle biopsies. Of the 69 cases, 23 cases(33.33%) were prostatic adenocarcinoma (PCa) and 46 cases(66.67%) were benign prostatic hyperplasia (BPH) .

In the present study, all the cases of BPH, with or without LGPIN, had been considered single group as previous studies suggest that prostate tissue diagnosed with low grade PIN are at no greater risk of having carcinoma on repeated biopsy19and foci of LGPIN did not show any difference in immunoreactivity for all the four IHC markers used in this study.

Peak incidence of carcinoma was noted in the age group between 61-70 years. Mean age of presentation of BPH cases was 67.8 years and that of PCa cases was 66.65 years. 8 cases of prostatic carcinoma fell in Gleason grade group V with scores 9 and 10.

Serum PSA values were available for 26 cases which include 18 malignant and 8 BPH cases. The highest S.PSA value observed in PCa cases was 709 ng/ml and the lowest value was 1.8 ng/ml. In BPH cases, the highest of the 8 available values was 14.5 ng/ml and lowest was 0.6 ng/ml.

P63 expression in study cases

All the malignant cases were immunonegative for p63. Whereas, 41 out of the 46 BPH cases showed strong and continuous nuclear positivity in basal cells. The rest 5 BPH cases were moderately positive for p63 in basal cell nuclei.

AMACR expression in study cases

21 out of total 23 PCa cases showed strong and diffuse cytoplasmic positivity for AMACR. 2 PCa cases showed moderate positive cytoplasmic staining. All the 46 BPH cases were immunonegative for AMACR. The relationship between AMACR expression and cases was assessed using Fisher's exact test. The statistic value of association obtained was <0.00001. The result is significant as p value is <0.05, which indicates a significant association of AMACR expression in PCa cases.

ER alpha expression in study cases

All the 69 cases included in the study expressed ERα in epithelial cells. 23 PCa and 42 BPH cases showed score of 4. 22 of 23 PCa cases and 45 of 46 BPH cases were also positive for ERα in stroma.

ER beta expression in study cases

18 of 23 PCa cases did not express ERβ in epithelial compartment whereas all the 46 BPH cases did express ERβ . 19 PCa cases did not

express ERβ in stroma, whereas, 45 out of 46 BPH cases were positive for stromal ERβ expression.

Table 1: Expression of ER alpha and beta in all the cases

HPE Diagnosis	ER alpha expression				ER beta expression			
	Epithelial		Stromal		Epithelial		Stromal	
	Positive	Negative	Positive	Negative	Positive	Negative	Positive	Negative
PCa	23	0	22	1	5	18	4	19
BPH	46	0	45	1	46	0	45	1

Table 2: Grading of ER alpha and beta markers

Scores	Grading of ER alpha positivity (epithelium)		Grading of ER alpha positivity (Stroma)		Grading of ER beta positivity (epithelium)		Grading of ER beta positivity (stroma)	
	PCa	BPH	PCa	BPH	PCa	BPH	PCa	BPH
0% (Score 0)	0	0	0	1	1	0	8	0
1 - 4% (Score1)	0	0	1	0	17	0	11	1
5 - 10% (Score 2)	0	1	1	2	0	0	2	10
11 - 20% (Score3)	0	3	1	6	1	2	2	21
>20% (Score 4)	23	42	20	37	4	44	0	14

The above table shows there is no significant correlation between the expression of the ER markers (p-value > 0.05) and the grades of PCa.

Table 3: Mann-Whitney U test for the markers based on malignancy (PCa and BPH)

	ER α in epithelium	ER α in stroma	ER β in epithelium	ER β in stroma
Mann-Whitney U	515.5	502	62	78.5
Asymp. Sig. (2-tailed)	0.863	0.731	0	0

The above table shows there is significant difference in the expressions of the marker, ER β in epithelium(U statistic= 62; P-value=0.000) and in stroma(U statistic=78.5; P-0 .000 value) in benign and malignant cases.This stands to prove that malignancy influences the expression of ER β,whereas such an influence is not seen in ER α in epithelium and ER α in stroma.

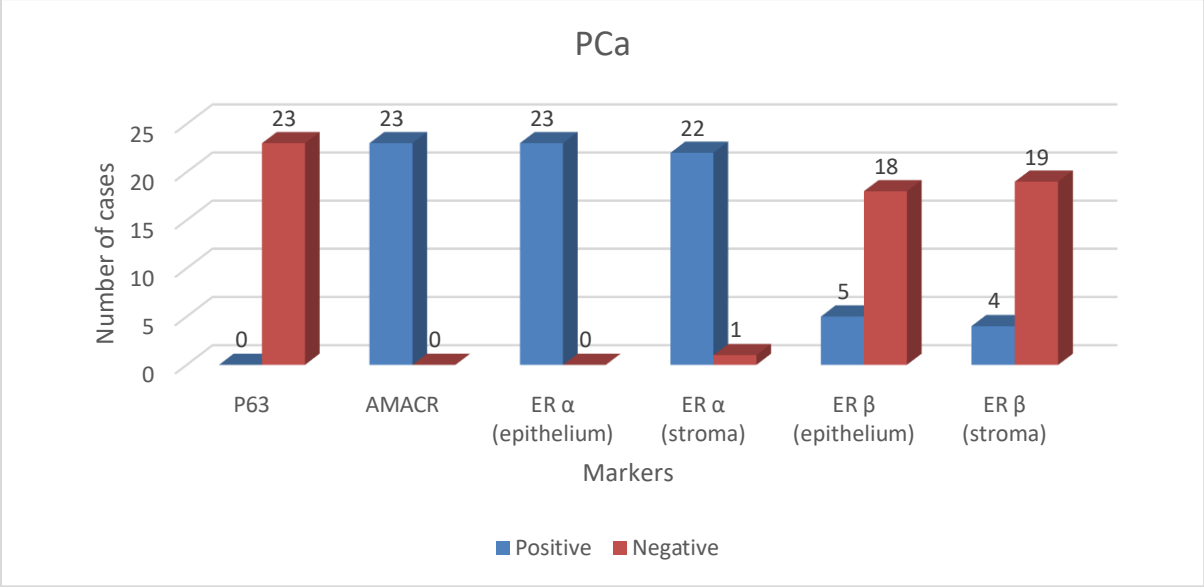

Figure 1: Distribution of positivity of the markers for PCa

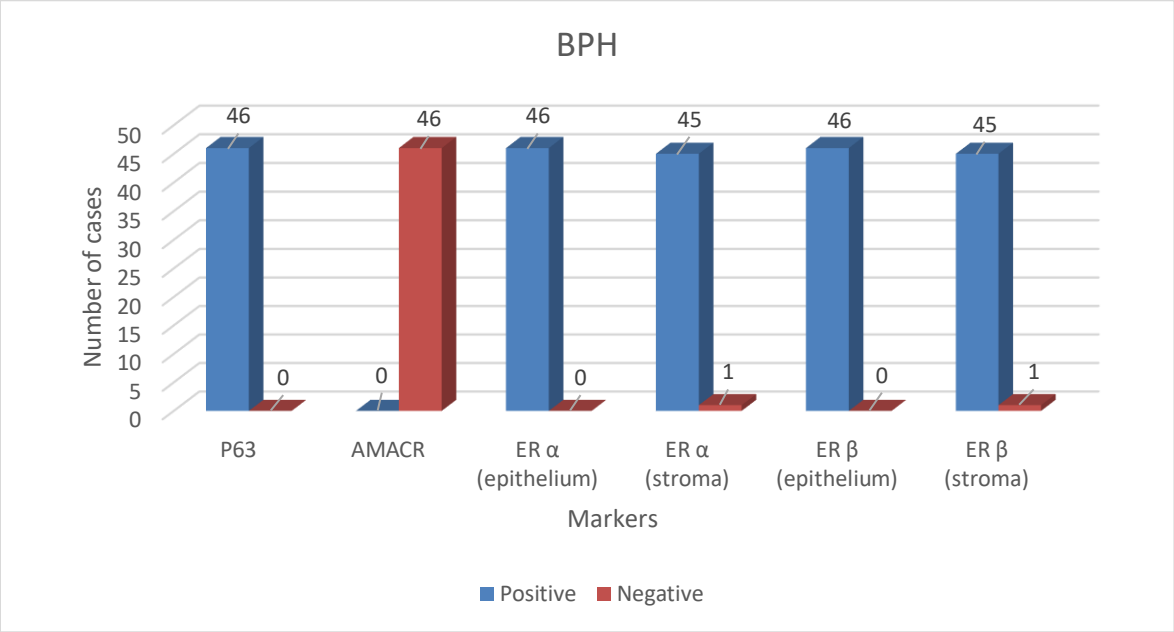

Figure 2: Distribution of positivity of the markers for BPH

The above charts show the significant difference in expression of ER beta in benign and malignant cases.

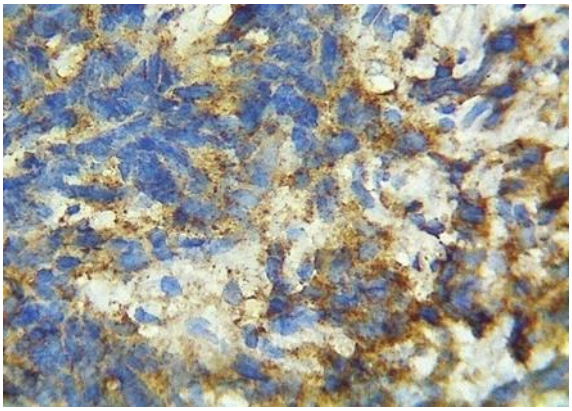

Fig 3: PCa with absent nuclear & cytoplasmic staining for ERβ

Discussion

The commonest Gleason grade group of malignant cases was grade group V, with Gleason scores of 9 & 10. Similar finding was observed in work done by Gabal SM et al[6]. Lower Gleason scores was common in study by Royuela MM et al[6] (Gleason score of 5-7), and Grindstad T et al[11]. Higher Gleason score expression may be due to late clinical presentation.

Serum PSA values were available for 26 cases which include 18 PCa cases and 8 BPH cases. The highest S.PSA value observed in PCa cases, was 709 ng/ml and the lowest value was 1.8 ng/ml. In BPH cases, the highest of the 8 available values was 14.5 ng/ml and lowest was 0.6 ng/ml. In the Spearman correlation test, S.PSA values did not show significant correlation with any of the clinicopathologic variables including Gleason grade and expression patterns of IHC markers.

p63 and AMACR immunostains showed 100% sensitivity, specificity, PPV and NPV in differentiating benign and malignant cases. The results are similar to studies done by Kalantari et al[19] on p63 andZhongjiang et al[20] on AMACR, respectively.

IHC with ERα and ERβ showed nuclear and cytoplasmic immunostaining of both epithelial and stromal cells in benign and malignant cases, a finding similar to few of the studies in literature[21,22]. Grindstad T et al11 and Horvath LG et al13 in their studies observed significant cytoplasmic staining of ERs, whereas Royuela MM et al[8] found an occasional cytoplasmic staining of ERs in their study, which was attributed to hormone binding transport proteins in cytoplasm.

ERα was expressed in epithelial cells in all the 69 cases studied, with 65 cases (94.2%) showing score 4 nuclear positivity. The ERα was expressed in 22 of 23 PCa cases and 45 of 46 BPH cases, with score 4 nuclear positivity in 57 of the 69 cases (82.6%). The statistic value of epithelial and stromal ERα expression were not significant. ERα in tumor stromal cells has been found to have a significant role in preventing metastases[23].

RoyuelaM et al[8] had observed significant more intense epithelial immunostaining in PCa cases. But our study showed no significant difference between malignant and benign cases. Daniels G et al[7] observed a lower ERα immunostaining in tumour stroma and Grindstad T et al11 observed no ERα staining in normal and tumour epithelium. These differences in staining patterns of ERα can be related to technical variations or increased expression in Asian men as quoted by some authors[24,25].

ERβ was not expressed in epithelial cells in 18 PCa cases and whereas it was expressed in all 46 BPH cases with score 4

immunostaining. The statistic test value was 0.000, indicating significant difference in expression of ERβ between PCa and BPH cases. Stromal ERβ expression was not seen in 19 PCa cases whereas 45 BPH cases expressed the same. The statistic value was significant with p =0.000. Spearman correlation test showed statistically significant correlation between epithelial and stromal ERβ expression in PCa cases with r = 0.624 and p 0.001.We had 5 malignant cases to be intensely positive for ERβ. Our study results on ERβ expression are similar to works done by Gabal SM et al[6] and Daniels G et al[7].Many studies show ERβ to be highly expressed in normal human prostate with progressive loss of expression in BPH and, to a greater extent, in PCa.13,27-30 In contrary, RoyuelaM et al[8] in their study had a result of increased epithelial ERβ immunostaining in PCa cases (79%) compared to BPH cases (30%)Some studies have shown increased expression of ERβ in malignant cases with metastasis[21]. However more number of cases may help substantiate it. ERβ agonists have been found to halt disease progression at early stages with improved survival rate. ERα was expressed both in benign and malignant lesions of prostate in both epithelial and stromal compartments. There was no difference in expression noted in our study. Further ERα staining in epithelial and stromal elements was statistically insignificant. But ERβ, which was expressed in nearly all benign cases in both compartments, was not expressed in majority of malignant cases. This loss of expression, which was statistically significant substantiates ERβ to be a more reliable immunohistochemical marker for diagnostic purposes. The variations in staining of ERβ in different studies emphasises the need to study its isoforms in pathophysiology of prostate. Recent studies have shown that ERβ2, an iso form has a role in migration and invasion by tumor cells apart from cell proliferation and differentiation[26,27]. It has also been shown to supress ERβ1 expression which promotes EMT[26].

Conclusion

Oestrogen receptors prove to play an important role in prostate tumorogenesis. It is believed that ER alpha has oncogenic and ER beta an antiproliferative role. The loss of expression of ERβ in malignant cases with statistical significance seems to make it a significant diagnostic marker compared to ERα in our study. ERβ may have an antiproliferative role in prostate carcinoma and may serve an effective target for newer therapeutic options. With recent studies focusing on molecular role of ER beta isofoms ,we need studies with such isoforms and larger sample size to support the hypothesis.

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