Original Article

Differences in SUV39H1 and Androgen Receptor Distribution in Adenomyomatous Hyperplasia and Prostatic Adenocarcinoma

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Abstract

Background: Androgen receptor (AR) contributes to the growth of both early- and late-stage prostate cancer. Overexpression of suppressor of variegation 3-9 homolog 1 (SUV39H1) increases migration of prostate cancer cells, while depletion of SUV39H1 suppresses migration of prostate cancer cells. **Aim:** In this study, the aim was to show the relationships of AR and SUV39H1 with adenomyomatous hyperplasia (AH) and prostate adenocarcinoma (PCa). **Materials and Methods:** 70 AH and 70 PCa preparations in Pathology Department from 2013 to 16 were retrospectively investigated. Samples with immunohistochemical staining for AR and SUV39H1 were evaluated with a light microscope. After pathologic investigation of samples, AR and SUV39H1 expressions were scored. The changes in the frequencies of the obtained scores in the AH and PCa groups were analyzed statistically. **Results:** AR expression was observed to be greater in AH compared to PCa. This difference was found to be statistically significant ($p = 0.003$). SUV39H1 expression was identified to be greater in PCa compared to AH and this showed statistical significance ($p = 0.031$). PCa samples were identified to have nearly 1.5 times more SUV39H1 mild staining compared to AH samples and this increase was two times for SUV39H1 strong staining. **Conclusion:** In our study, AR expression was greater in AH compared to PCa samples. This situation is inverse to the known mechanism and cannot be clearly explained. It needs to be supported with large series and other prognostic parameters. This study observed increased SUV39H1 values in PCa compared to AH and from this aspect, it may be considered an important poor prognosis parameter.

Keywords: *Adenomyomatous hyperplasia, androgen receptor, prostate adenocarcinoma, prostate, SUV39H1*

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Introduction

The prostate is the organ showing the most common neoplastic transformation in the human body, and these transformations may be benign or malignant (prostate carcinoma).[1]

Benign prostate hyperplasia (BPH) is the non-malignant expansion of the prostate due to cellular hyperplasia.[2] BPH generally develops from the transitional zone of the prostate and causes problems by obstructing urine flow.[3]

Prostate cancer is one of the most common cancers observed in males and the incidence increases with increasing age.[4] Prostate cancer is an androgen-dependent disease and it is considered that in the next 10 years this cancer will be first among the leading causes of cancer-linked deaths in males.[5] Development and progression of prostate carcinoma are linked to androgenic stimulation.[6] Hormone-refractory prostate cancer frequently recurs and may cause bone metastasis. At this stage, treatment of the disease becomes more difficult.[7]

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Androgen receptor (AR) (NR3C4, nuclear receptor subfamily 3, group C, gene 4) belongs to the steroid hormone group of nuclear receptors with estrogen receptors, glucocorticoid receptors, progesterone receptors, and mineralocorticoid receptors.[8-10] Additionally, it is a ligand-dependent transcription factor controlling the expression of androgen-responsive genes. An important step in androgen action amplifying castration-resistant prostate cancer is a nuclear translocation of AR.[11]

The basis of physiologic functions of androgens is linked to ARs, a member of the binding, 110 kDa weight, protein, and nuclear receptor subfamily.[12-15] This receptor is localized to the q branch of the X chromosome (Xq11.2).[6] AR is a ligand-dependent transcription factor controlling the expression of specific genes.[16,17] AR is necessary for prostate development and normal prostate function.[4,18] In the prostate, AR is expressed in both the luminal layer of the epithelium and in stromal tissues.[6,19] In BPH and PCa, it is notable that the epithelial AR effect is greater than mesenchymal AR.[20] AR plays a role in the initiation and progression of a variety of cancer types (bladder, kidney, lung, breast, and liver, but not the prostate, where it acts as a suppressor). Among a variety of tumor types in a tissue or organ, AR expression levels may display differences.[21]

AR signals may be associated with urothelial cancer development and urothelial cancer progression. AR signals mediate the biological effects of androgens in different physiologic and pathologic processes as a result.[22] AR and modulators of AR activity are important in prostate cancer.[23] Multiple forms of AR were found to contribute to the growth of both early- and late-stage prostate cancer.[24] AR is a ligand-inducible transcription factor in the nuclear hormone receptor superfamily playing a critical role in the initiation, growth, and progression of the tumor in prostate cancer.[25-27]

When prostate cancer is identified early, curative treatments like surgery and radiotherapy are permitted. Patients with prostate carcinoma may be treated with androgen ablation therapy.[28] Changes in AR signal in surrounding stroma affect tumor cell behavior to a significant degree. There is a strong connection between stromal AR expression and patient outcomes. As a result, it was identified that treatments targeting the stroma may be effective.[29] As a result, therapies targeting the AR signal axis provide effective first-stage treatment for advanced PCa.[27,30]

Immunohistochemical (IHC) studies have shown that AR expression is heterogeneous in prostate cancer.[18] Prostate cancer animal model reported that increased AR expression may begin the development of prostate cancer.[31] The reason for the loss of AR expression in some cells in tumor foci was found uncertain.[32-34] Androgen activation is associated with urothelial carcinogenesis and tumor growth.[23] Stromal AR has been reported to play an important role in the progression of prostate diseases (BPH and PCa).[19]

The suppressor of variegation 3-9 homolog 1 (SUV39H1) is a histone methyl transferase containing a prototype SET-domain.[35,36]

In humans, histone H3 lysine 9 methylation (H3K9me) is mostly based on SUV39 family members; in other words, SUV39H1, SUV39H2, GLP, G9a, SET-domain bifurcated histone lysine methyltransferase 1 (SETDB1), and SETDB2. All of these enzymes have a highly preserved catalytic region containing Pro-SET, SET, and SET-SET domains.[37]

Histone H3 lysine 9 trimethylation (H3K9me3) is specifically catalyzed via trimethylation and regulates global levels.[35,36] H3K9me3 plays an important role in heterochromatin formation and basic cellular processes.[38]

SUV39H1 has an important role in hepatocellular carcinoma (HCC) development and progression through H3K9me3. The SUV39H1 and H3K9me3 correlation may be a marker to be kept in mind for HCC recurrence. SUV39H1 is expressed at high rates in the nuclei of HCC cells; however, it is not reported to be expressed in the cytoplasm.[39] There was a reduction in SUV39H1 levels identified in the pulmonary tissue of cases with chronic obstructive pulmonary disease.[40]

Overexpression of SUV39H1 does not affect the proliferation of prostate carcinoma. Overexpression of SUV39H1 increases the migration of prostate cancer cells, while SUV39H1 depletion suppresses prostate cancer cell migration. There is a positive correlation between SUV39H1 expression and the pathologic stage of PCa. In a study, the novel target of SUV39H1 was proposed to inhibit PCa cell migration. Yu *et al*.[41] proposed that SUV39H1 should be targeted as a new strategy to reduce prostate cancer cell migration and invasion.

In this study, the aim was to reveal the importance of AR and SUV39H1 expression in prostate tissues.

Materials and Methods

Before beginning the study, permission was granted by the Clinical Research Ethics Committee dated 02/11/2015 and numbered 2015/14.

This study used preparations with adenomyomatous hyperplasia (AH) and prostate adenocarcinoma (PCa)

diagnosis from 2013 to 16 in Ordu Training and Research Hospital Pathology Department. Preparations were removed from the archive and re-evaluated in line with the study aims. New sections with 3 μm thickness were obtained from paraffin blocks of the collected prostate tissues, and IHC staining was performed with a Leica Bond automatic tissue staining device for AR (SP107) C.Liq. 0.1 mL (1:50–200) and SUV39H1 (Polyclonal) C.Liq. 0.1 mL (1:100–200). Stained samples were assessed with a light microscope. AR and SUV39H1 expression were semi-quantitatively assessed according to staining intensity with four staining levels of none, mild, moderate, and strong (0–3+).[42,43]

Statistical Analysis of Data

Data obtained in the study are stated as frequency. Statistical calculations in the research were completed with the statistical package for social sciences version 22.0 (IBM Corp, Chicago, IL, USA) software. Chi-square analysis was used for the assessment of data. In Chi-square tests, if the expected frequency was ≥5 Pearson's Chi-square value (χ^2) was calculated, while for values <5 likelihood ratio Chi-square value ($LR\chi^2$) was calculated. The dependence rate in situations where a correlation was found between variables as a result of Chi-square tests was determined with the contingency coefficient.

For statistical analyses and interpretations, 5% of significance level was noted.

Results

In the Pathology Department, 70 AH and 70 PCa cases from 2013 to 16 were accessed and included in the evaluation. After pathologic investigation of samples taken from patients, the distribution of AR staining results (none, mild, moderate, and strong) in AH and PCa cases is given in Table 1.

According to Table 1, the distribution of AR staining results (none, mild, moderate, and strong) in AH and PCa cases after pathologic investigation of samples taken from patients showed statistically significant variation ($p = 0.003$). In AR staining results, the AH and PCa distribution dependence rate was calculated as 28.4% ($p < 0.001$). AH was identified to have nearly two times more AR mild staining compared to PCa samples. Similarly, the AR strong staining rate in AH samples was observed to be nearly 1.5 times greater than for PCa samples. Unlike these, PCa was identified to have nearly two times more AR moderate staining compared to AH samples.

The distribution of SUV39H1 staining results (none, mild, moderate, and strong) in cases with AH and PCa is given in Table 2 [Figures 1-6].

According to Table 2, the distribution of SUV39H1 staining results (none, mild, moderate, and strong) in AH and PCa cases after pathologic investigation of samples taken from patients showed statistically significant variation ($p = 0.031$). The correlation between AH and

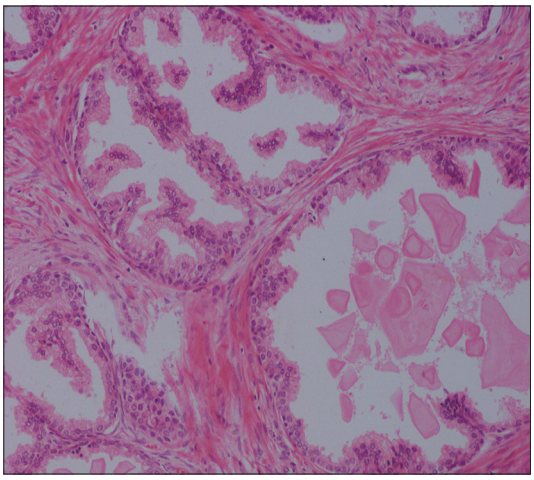

Figure 1: AH, hematoxylin and eosin (H&E ×200)

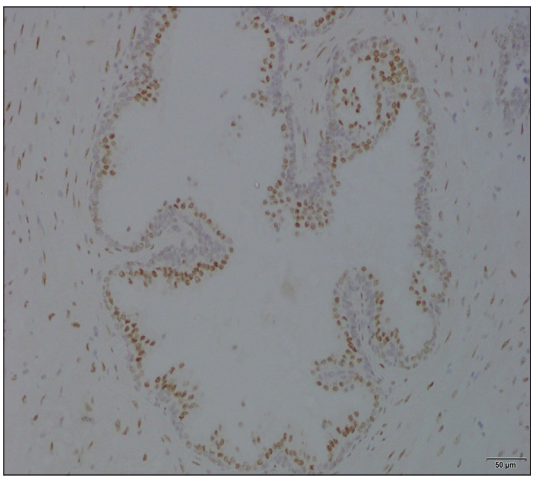

Figure 2: AH, AR×200 (Staining score: 3)

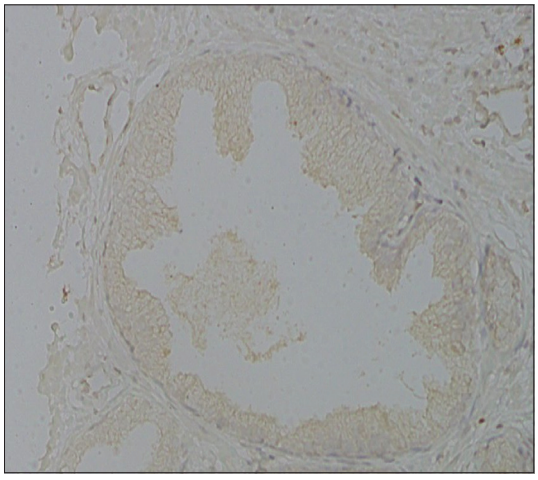

Figure 3: AH, SUV39H1×200 (Staining score: 2)

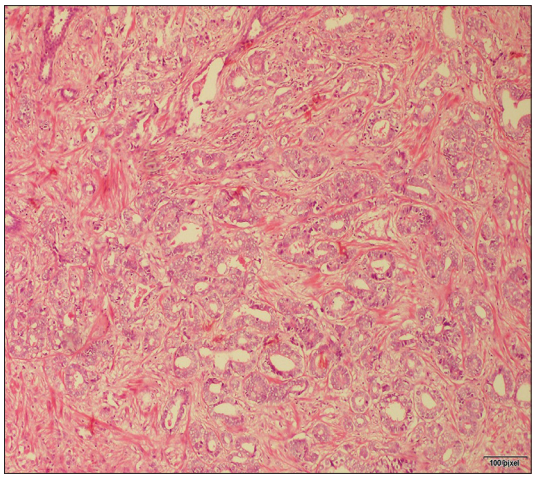

Figure 4: PCa, H&E×200

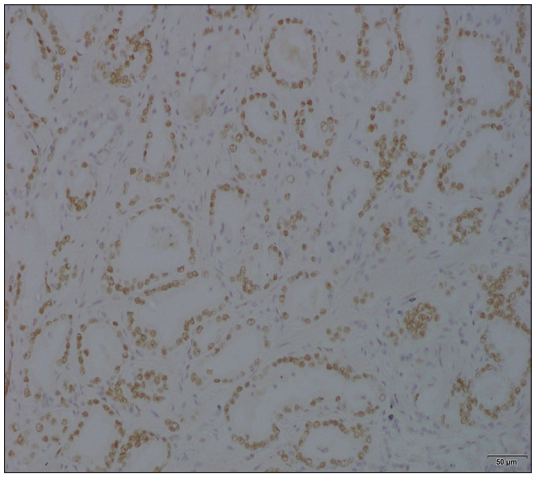

Figure 5: PCa, AR×200 (Staining score: 3)

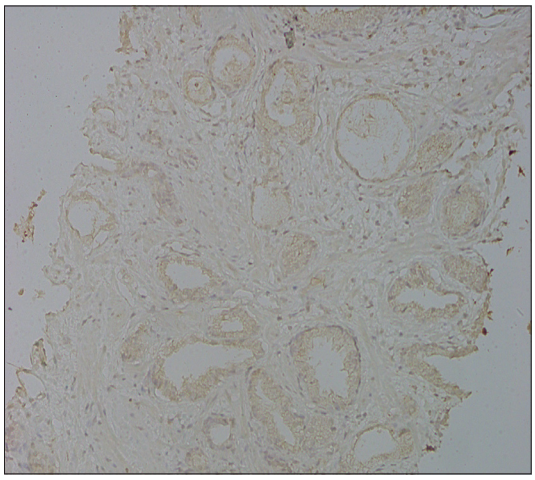

Figure 6: PCa, SUV39H1×200 (Staining score: 2)

PCa and staining results was calculated as 25.4% and found to be statistically significant ($p < 0.05$). PCa samples were identified to have nearly 1.5 times more SUV39H1 mild staining compared to AH samples and this increase was two times for SUV39H1 strong staining. SUV39H1 none and moderate staining were observed at higher rates in AH samples. However, SUV39H1 none and moderate staining were observed at higher rates in AH samples. It was found to be nearly 2.3 and 1.4 times more than in PCa samples.

Table 1: Dependence results for AR staining according to AH-PCa status

Type	Staining				Total
	None	Mild	Moderate	Strong	
AH					
n (%)	0 (0.0)	4 (5.7)	19 (27.1)	47 (67.1)	70 (100.0)
PCa					
n (%)	5 (7.1)	2 (2.9)	32 (45.7)	31 (44.3)	70 (100.0)
Total					
n (%)	5 (3.6)	6 (4.3)	51 (36.4)	78 (55.7)	140 (100.0)
LR χ^2=14.267; CC=0.284; *P*=0.003**					

LR χ^2=Likelihood ratio Chi-square, CC=Contingency coefficient, ***P*<0.01. (AR=Androgen receptor, AH=Adenomyomatous hyperplasia, PCa=Prostate adenocarcinoma)

Table 2: Dependence results for SUV39H1 staining according to AH-PCa status

Type	Staining				Total
	None	Mild	Moderate	Strong	
AH					
n (%)	18 (25.7)	20 (28.6)	22 (31.4)	10 (14.3)	70 (100.0)
PCa					
n (%)	8 (11.4)	26 (37.1)	16 (22.9)	20 (28.6)	70 (100.0)
Total					
n (%)	26 (18.6)	46 (32.9)	38 (27.1)	30 (21.4)	140 (100.0)
χ^2=8.909; CC=0.245; *P*=0.031*					

χ^2=Pearson's Chi-square, CC=Contingency coefficient, **P*<0.05. (AH=Adenomyomatous hyperplasia, PCa=Prostate adenocarcinoma)

Discussion

In this study, AH was identified to have two times AR mild staining intensity compared to PCa samples. Similarly, in AH samples AR strong staining rates were observed to be nearly 1.5 times greater than in PCa samples.

In our study, AR expression is considered to be due to higher observation of heterogeneity in AH compared to PCa. A study by Bass *et al*.[44] similarly showed lower AR expression in prostate cancer cells compared to benign prostate cells. There are similar[44] and different[18,23,45] studies related to AR expression found. As this study was retrospectively planned, serum AR levels were not examined. A prospective study with correlated results for AR levels may be more enlightening. Additionally, in PCa AR expression is reduced and it is suggested that this reduction may be associated with heterogeneity.

Studies related to SUV39H1 staining reported that SUV39H1 plays an important role in tumorigenesis of a variety of types of cancer.[39,46] Chen *et al*.[40] showed reduced SUV39H1 levels in pulmonary tissue of cases with chronic obstructive pulmonary disease. Chiba *et al*.[39] identified that SUV39H1 was expressed at very high rates in the nuclei of HCC cells; however, it was not expressed in the cytoplasm. The researchers stated that SUV39H1 had an important role in the development and progression of HCC through H3K9 trimethylation. According to another study, SUV39H1 was stated to have an antimigratory role in cervical cancer.[47] Lu *et al*.[48] found significantly high levels of SUV39H1 in colon carcinoma. When the literature is examined, it is notable that the prognostic significance of SUV39H1 is controversial. There are similar[41,48] and different[47] studies found related to SUV39H1 expression.

In this study, similarly, PCa samples were observed to have 1.5 times greater SUV39H1 mild staining compared to AH samples and this increase was determined to be two times for SUC39H1 strong staining.

In conclusion, in this study, the SUV39H1 values in PCa showed increased expression compared to AH and it is considered it may be important as a poor prognosis parameter in this respect.

In our study, AR expression was greater in AH compared to PCa samples. This situation is inverse to the known mechanism and cannot be clearly explained. It needs to be supported with large series and other prognostic parameters.

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Conflicts of interest

There are no conflicts of interest.

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