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Expression of Transforming Growth Factor β Type I and II Receptor in Prostate Cancer

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Abstract:

This study was carried out to establish the correlation between expression of Transforming growth factor beta receptor one (TGF-βRI) and Transforming growth factor beta receptor two (TGF-βRII) and prostate cancer progression, and to establish the role of prostate cancer development. Immunohistochemistry (IHC) technique was used to detect the level of expression of TGF-βRI and TGF-βRII protein in tissues of patients and healthy control groups. TGF-βR1 protein was expressed in 3 (18.7%) and 14 (56%) of poorly and moderately differentiated malignancy respectively. There was significant difference in mean level of TGF-βRI protein expression among all studied groups. TGF-βRII protein was expressed in 6 (37.5%) and 22 (88%) of poorly and moderately differentiated malignancy respectively, There was significant difference in mean level of TGF-βRII protein expression among all studied groups. We concluded that there was statistically significant association between the loss of expression of TGF-β1 signaling receptors, especially TGF-βRI, and increasing grades of malignancy in prostate cancer, leading to a more malignant phenotype.

Keywords: *TGF-βRI, TGF-βRII, prostatic hyperplasia, moderate, benign, prostate cancer, malignancy.*

Introduction:

Prostate cancer is a cancer that arises in the prostate .The prostate, is a gland of man reproductive system. The primary function of prostate gland is to secrete a fluid that is added together with spermatozoa from the seminal vesicles to constitute the majority of semen (1). Prostate cancer is the second cancer causing death in men, after lung cancer (2). Prostate tumors are usually slow growing and symptoms may not occur for many years (3). In early stages of prostate cancer, there are usually no symptoms. If the cancer is advanced, it can spread to other organs, causing bone pain in the pelvis or ribs. Many of urinary symptoms also occur in other prostate diseases, like benign prostate hyperplasia and an enlargement of the prostate gland (4). Inflammation of prostate area causes a novel putative prostate cancer precursor lesion called proliferative inflammatory atrophy (PIA), which shares some molecular traits with prostate intraepithelial neoplasia and PCa (5).

TGF-βI is a pleiotropic growth factor that has been implicated in multiple and often diametrically opposed functions including proliferation, differentiation, and apoptosis (6). In cancer cells, TGF-β acts as a growth promoter and aids in metastasis, but it appears to inhibit cell growth and induce apoptosis in normal cells (7). Characteristics of aggressive prostate cancer (PCa) include a gradual loss of sensitivity to TGF-β and over-expression of TGF-β, which appears to initiate a vicious cycle for tumor progression. Although it is noticed that loss of expression of TGF-β receptors (TGF-βRs) enable cancer cells to escape the growth inhibitory effect of TGF-β and to gain a growth advantage, but the mechanism(s) underlying these events in human (PCa) cells remains undefined (8).

The TGF-βRI gene provides instructions for making a protein called transforming growth factor-beta (TGF-β) receptor type I. This receptor transmits signals from the cell surface into the cell through a process called signal transduction. In this type of signaling, the environment outside the cell influence activities inside the cell such as stimulation of cell growth and division (9). Transforming growth factor beta receptor II (TGF-βRII) is a transmembrane protein that has an intrinsic serine-threonine kinase activity and signals through a heterodimeric complex with another receptor protein (TGF-βRI) that binds TGF-beta (10).This receptor/ligand complex phosphorylates proteins then enter the nucleus and regulate the transcription of a subset

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of genes that are related to cell proliferation.

The study aimed To study the expression of certain immunological markers (TGF-beta one (TGF-βI) and TGF-beta receptors one and TGF-beta receptors two) in the epithelial and stromal compartments of prostate carcinoma, benign prostatic hyperplasia, and normal prostate tissue.

Materials & Methods:

The study encompassed 107 prostate tissue samples of 41 prostate cancer patients and 46 benign prostate hyperplasia . They were diagnosed by the consultant pathologists at Baghdad Hospital for Specialist Surgeries, Al-Yarmook Teaching hospital, and AL-Hilla teaching hospital, and 20 normal prostate samples by autopsy at institute of forensic. Each patient and normal prostate tissue sample restored in 10% buffer formalin and instilled in paraffin wax and then cut into 4µ-thick sections and put on ordinary slide and stained with Haematoxylin-eosin stain and examined under microscope by two independent pathologist to characterized tumor grade. Then cut another 4µ-thick section and put on positively charged slide to detect the expression of the following immunological markers (TGF-β I and II receptors)by using Immunohistochemical technique .

This technique is based on the detection of the product of a gene expression (protein) in malignant, benign and normal tissues using specific monoclonal antibodies (i.e) primary antibody (Ab) for specific epitope (mouse monoclonal Abs for TGF-βRII), and primary Ab for specific epitope (Rabbit monoclonal Abs for TGF-β RI) , this then binds to cytoplasmic target protein . The bound primary Ab is then detected by a secondary Ab, which contain a specific label. The secondary Ab is then detected by a detection system specific for the label3, 3-diaminobenzidine (DAB) in a chromogen solution. The cut-off for positivity was 10% for (TGF-βRI and TGF-βRII). Quantitative IHC scoring was evaluated by counting the number of positive and negative cell cytoplasm in several randomly selected fields in each section. The percentage of positive expression of each marker in the cells was calculated as following. For all studied markers, the positivity of scoring as, 0: No reaction; (<10%): Weak reaction; (10-50%): Moderate reaction; and(>50%): Strong reaction. (11, 12)

Statistical analysis:

The significance of difference of different means (quantitative data) were tested using T- test for difference between two independent means or ANOVA test for difference among more than two independent means. The significance of difference between different percentages (qualitative data) was tested using Pearson's chi square test (X2 test).Pearson correlation was calculated for the correlation between two quantitative variables with its t-test for testing the significance of correlation. The correlation coefficient value (r) either positive (direct correlation) or negative (inverse correlation) with values <0.3 represent no correlation, 0.3-<0.5 represent weak correlation, 0.5-<0.7 moderate strength, >0.7 strong correlation.Statistical significance was considered whenever the P value for the test of significance was equal or less than 0.05.

Results:

This study included (87) prostate sample tissue from Iraqi patients with prostate cancer and benign prostatic hyperplasia . They were divided into three groups , in which 16 (14.9%) patients were with poorly differentiated malignancy . 25 (23.3%) patients with moderately differentiated malignancy according to the Gleason scoring system , 46 (43.0%) patients with benign prostatic hyperplasia ,and there were 20 (18.6%) normal prostate tissue.

All tissue samples were used to study the expression of transforming growth factor beta receptor one (TGF- βRI) and transforming growth factor beta receptor two (TGF- βRII),by immunostaining analysis, using specific monoclonal antibodies for markers.

TGF-βRI protein was expressed in (83) patients (77.5%) with moderate expression being the most frequent score among the total cases (43.9%), and the results showed that the negative immunostaining reaction was the most frequent scores of TGF- βRI expression among both poorly and moderately differentiated malignancy group (81.2%),(44.0%) respectively, while moderate immunostaining reaction being the most frequent score among benign prostatic hyperplasia group(82.6%). In normal prostate tissue, strong immunostaining reaction was the most frequent score (85.0%). While the weak immunostaining reaction observed in poorly differentiated malignancy represented by 3 samples (18.7%) in score of <10% positive cells .Table (1).

Table -2 : Statistical analysis of TGF-βRI immunoexpression and the difference in it's expression among different studied subjects

TGF-βRI % IHC Score	Poorly Differentiated Malignancy	Moderately Differentiated Malignancy	BPH	Normal	Total
NO. 0٪	13 (81.2)	11 (44.0)	0 (0.0)	0 (0.0)	24 (22.4)
NO. 10% > %	3 (18.7)	8 (32.0)	0 (0.0)	0 (0.0)	11 (10.2)
NO. 10-50% %	0 (0.0)	6 (24.0)	38 (82.6)	3 (15.0)	47 (43.9)
NO. >50%	0 (0.0)	0 (0.0)	8 (17.3)	17 (85.0)	25 23.3))
NO. Total %	16 (14.9)	25 (23.3)	46 (43.0)	20 (18.6)	107 (100.0)

Statistical analysis of TGF-βRI immunoexpression and the difference in its expression among different studied subjects.

There was significant difference in mean level of TGF-βRI protein expression between each of poorly differentiated malignancy, moderately differentiated malignancy, and benign prostatic hyperplasia groups as compared to normal prostate tissue group, with p value of (0.0001). Also there was significant difference in mean level of TGF-βRI protein expression between each of poorly differentiated malignancy and moderately differentiated malignancy group as compared to benign prostatic hyperplasia group, with P value of (0.0001).In comparing poorly differentiated malignancy group with moderately differentiated malignancy group there was also significant difference between them in mean level of TGF-βRI protein expression at P value of (0.0001).Table (2), Figure (1).

Also there was significant difference in mean level of TGF-βRI protein expression among all studied subjects with P value of (0.0001), by using ANOVA test. Figure(2).

Table -2: Statistical analysis of TGF-βRI immunoexpression and the difference in it's expression among different studied subjects

TGF-βRI% Average		Poorly Differenti-atedMalignancy	Moderately Differ-entiated Malig-nancy	BPH	Normal
	Number	16	25	46	20
	Mean±SD	1.4±3.0	8.4±11.6	34.7±10.3	52.2±8.1
	Standard Error of Mean	0.741	2.325	1.514	1.810
	Range	0-8.0	0-40.0	23.0-60.0	31.0-60.0
	Percentile 05th	0	0	24.0	33.5
	25th	0	0	28.0	51.0
	50th (Median)	0	5.0	30.5	54.0
	75th	0	9.0	35.0	58.0
	95th	8.0	32.0	56.0	60.0
	99th	8.0	40.0	60.0	60.0
P value compare to Normal		0.0001*	0.0001*	0.0001*	-
P value compare to BPH		0.0001*	0.0001*	-	-
P value compare to Moderately Differenti-ated Malignancy.		0.0001*	-	-	-
P value comparing all		0.0001#	-	-	-
*Significant difference between two independent means using Students-t-test at 0.05 level					
#Significant difference among three independent means using ANOVA test at 0.05 level					

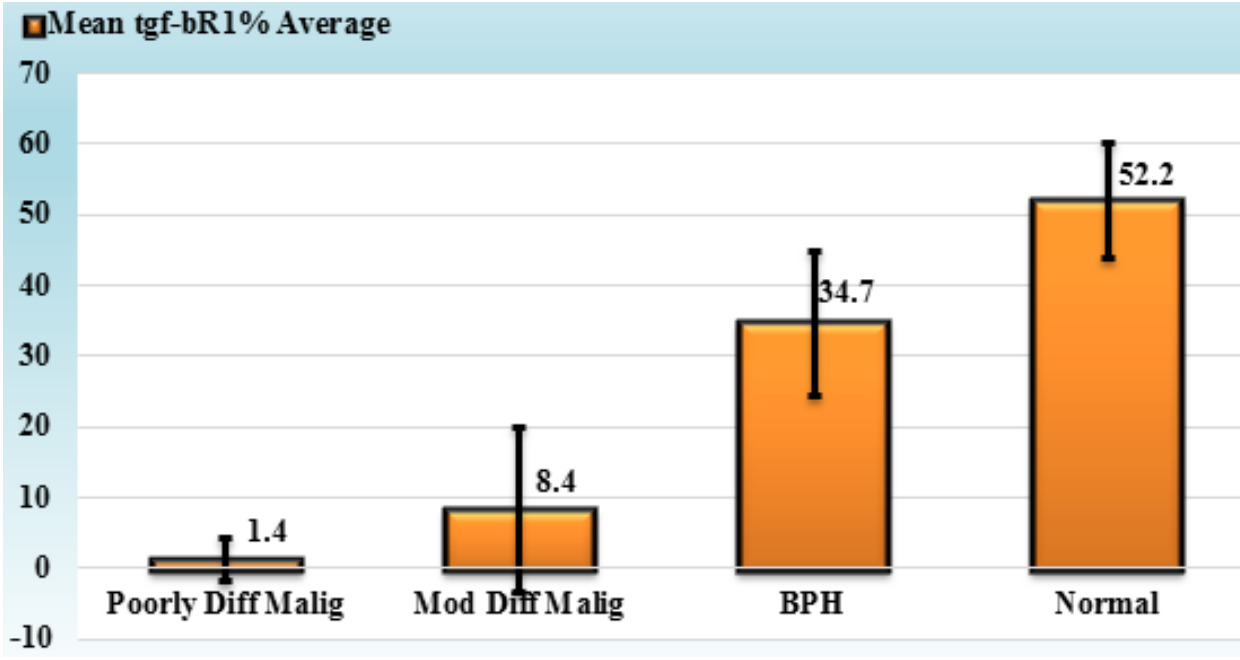

Figure 1: Descriptive differential analysis and differences in means level of TGF-βRI protein expression between each studied subjects.

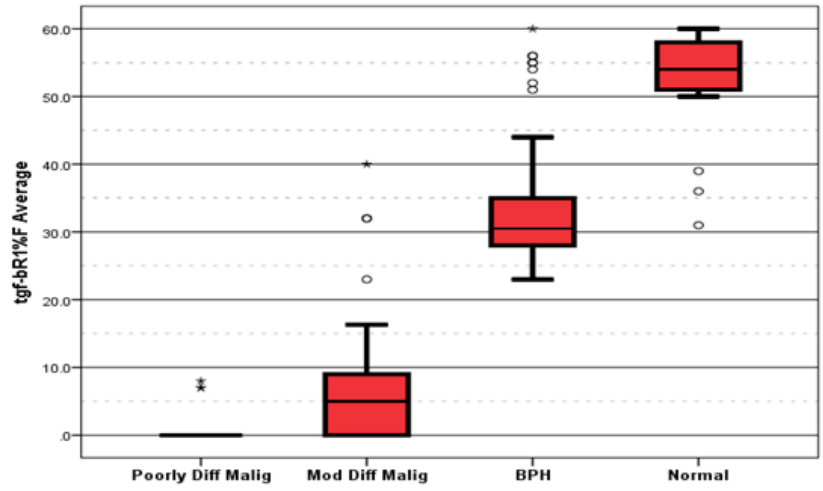

Figure 2: (Box Blot), Differences in mean level of TGF-βRI protein expression among all studied subjects,by using ANOVA test.

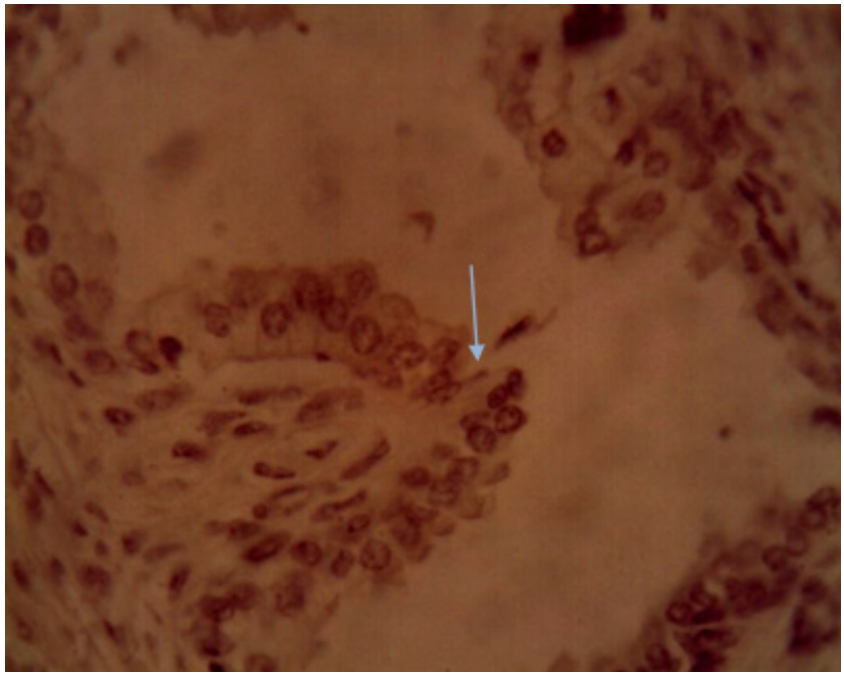

Figure – 3: Immunohistochemical staining of TGF-βRI in Benign Prostatic Hyperplasia within the cytoplasm of benign cells (white arrow), moderate reaction,X100

Transforming growth factor beta receptor two (TGF-βRII):

Frequency of transforming growth factor beta receptor two(TGF-βRII) IHC scores in study subjects:

TGF-βRII protein was expressed in 94 (87.8%) prostate tissue samples, with moderate score of expression being the most frequent score among the total cases (37.3%).

TGF-βRII protein was expressed in all prostate tissue, with moderate immunostaining reaction being the most frequent score among benign prostatic hyperplasia group (65.2%),and weak immunostaining reaction being the most frequent score among moderately differentiated malignancy group (72.0%) . In poorly differentiated malignancy, negative immunostaining reaction was the most frequent score (62.5%),but in normal prostate tissue strong immunostaining reaction for TGF-βRII was the most frequent score (70.0%). Table (3).

Table- 3: Frequency table of TGF-BRII Immunohistochemistry scores in study subjects.

TGF-βRII% IHC Scores	Poorly Differentiated Malignancy	Moderately Differentiated Malignancy	BPH	Normal	Total
.NO **%0** ٪	10 (62.5)	3 (12.0)	0 (0.0)	0 (0.0)	13 (12.1)
.NO **< 10%** ٪	6 (37.5)	18 (72.0)	8 (17.3)	0 (0.0)	32 ((30.0
.NO ٪ **10-50%**	0 (0.0)	4 (16.0)	30 (65.2)	6 (30.0)	40 (37.3)
.NO **%>50%**	0 (0.0)	0 (0.0)	8 (17.3)	14 (70.0)	22 (20.5)
NO. Total ٪	16 (14.9)	25 (23.3)	46 ((43.0	20 (18.6)	107 (100)

The statistical analysis of TGF-βRII immunoexpression and the difference in its expression among different studied subjects.

There was significant difference in mean level of TGF-βRII protein expression between each of poorly differentiated malignancy ,moderately differentiated malignancy and benign prostatic hyperplasia groups as compared to normal prostate group, with P value of (0.0001) . In comparing each of poorly differentiated malignancy and moderately differentiated malignancy group with benign prostatic hyperplasia group, there was significant difference in mean level of TGF-βRII protein expression with P value of (0.0001). Also in comparing poorly differentiated malignancy group with moderately differentiated malignancy group,there was significant difference in mean level of TGF-βRII protein expression with P value of (0.0001). Table(4), Figure (4).

Also there was significant difference in mean level of TGF-βRII protein expression among all studied subject with P value of (0.0001), by using ANOVA test. Figure (5).

Table 4 : The statistical analysis of TGF-βRII immunoexpression and the difference in it's expression among different studied groups.

TGF-βRII% Average		Poorly Differentiated Malignancy	Moderately Differentiated Malignancy	BPH	Normal
	Number	16	25	46	20
	Mean±SD	2.8±3.9	10.6±11.0	26.0±15.7	52.2±6.8
	Standard Error of Mean	0.971	2.199	2.322	1.518
	Range	0-9.0	0-43.0	8.0-60.0	38.0-71.0
	Percentile 05th	0	0	9.0	41.5
	25th	0	5.0	14.0	47.5
	50th (Median)	0	8.0	20.0	52.0
	75th	8.0	9.0	37.0	56.0
	95th	9.0	36.0	52.0	65.5
	99th	9.0	43.0	60.0	71.0
P value compare to Normal		0.0001*	0.0001*	0.0001*	-
P value compare to BPH		0.0001*	0.0001*	-	-
P value compare to Moderately Differentiated Malignancy.		0.0001*	-	-	-
P value comparing all		0.0001#	-	-	-
*Significant difference between two independent meansusing Students-t-test at 0.05 level					
#Significant difference among three independent means using ANOVA test at 0.05 level					

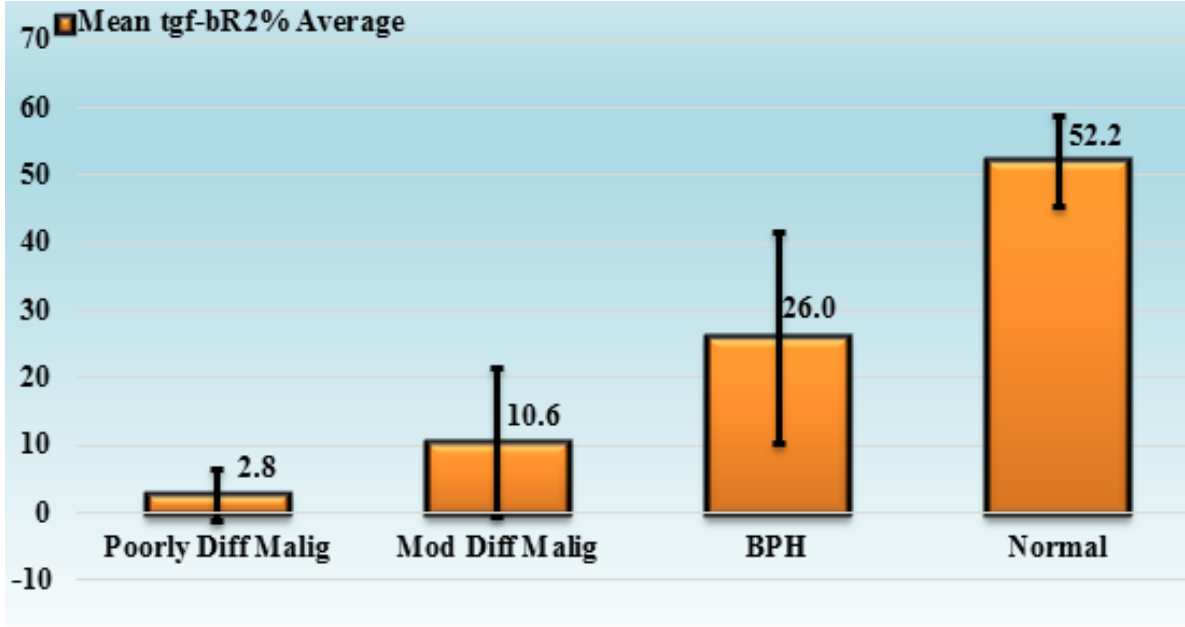

Figure - 4: Descriptive differential analysis and differences in means level of TGF-βRII expression between each studied groups.

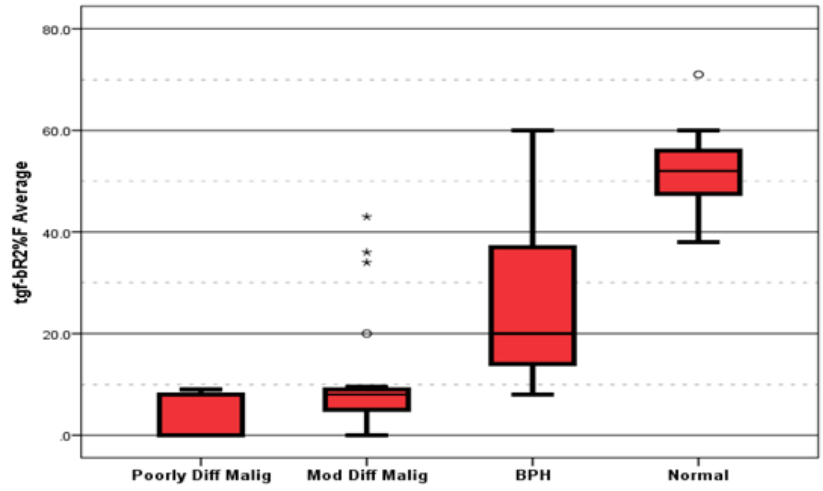

Figure - 5: (Box Blot), Differences in mean level of TGF-βRII protein expression among all studied subjects, by using ANOVA test.

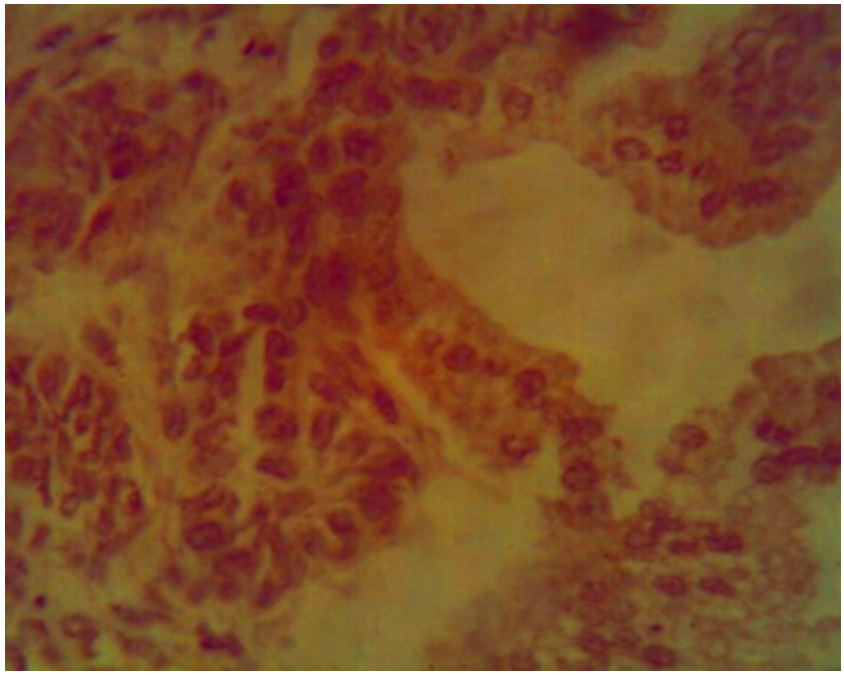

Figure -6: Immunohistochemical staining of TGFβRII protein in moderately differentiated prostatic carcinoma within the cytoplasm of malignant cells (white arrows), moderate reaction, X100.

Correlation coefficient of different study markers to each other in poorly differentiated malignancy patients.

Table - 5: Correlation coefficient of different study markers to each other in poorly differentiated malignancy group

Poorly Differentiated Malignancy		TGF-βRI% Average	TGF-βRII% Average
TGF-βRI% Average	**r**	-	-0.196
	p	-	0.467
TGF-βRII% Average	**r**	-0.196	-
	p	0.467	-

**Correlation is significant at the 0.01 level.

Correlation coefficient of different study markers to each other in moderately differentiated malignancy group.

There was direct association between TGF-βRI and TGF-βRII immunoexpression in moderately differentiated malignancy by means of RS= 0.917, withP value of =0.0001. Table (4).

Table 6: Correlation coefficient of different study markers to each other in moderately differentiated malignancy group

moderately Differentiated Malignancy		TGF-βRI% Average	TGF-βRII% Average
TGF-βRI% Average	**r**		0.917**
	p		0.0001
TGF-βRII% Average	**r**	0.0001	-
	p	0.917**	-

**Correlation is significant at the 0.01 level.

Correlation coefficient of different study markers to each other in patients with benign prostatic hyperplasia:

There was direct association between TGF-βRI and TGF-βRII immunoexpression by means of RS= 0.744 with P value of 0.0001. Table(5).

Table 7: Correlation coefficient of different study markers to each other in patients with benign prostatic hyperplasia.

benign		**TGF-βRI% Average**	**TGF-βRII% Average**
TGF-βRI% Average	r	-	0.744**
	p	-	0.0001
TGF-βRII% Average	r	0.744**	-
	p	0.0001	-

**Correlation is significant at the 0.01 level.

Discussion:

Transforming growth factor beta (TGF-β) is a prototypical member of a superfamily of multifunctional cytokines that plays an important role in the inhibition of epithelial cell proliferation. TGF-βI initiate its effects by binding to specific cell-surface type II receptors (13), which are constitutively active transmembrane serine/threonine kinases that recruit TGF-βRI and phosphorylate one or more substrates to initiate a signal cascade such as that of (Smad) proteins (14) The presence of both TGF-βRI and TGF-βRII is necessary to effect a TGF-β response, and both receptor activities must be functional for proper signal transduction (13).

The TGF-βRI gene present in malignant prostate cells results in reduced expression of TGF-βRI protein (15). Mutations in TGF-β-related genes appear to be closely linked to the progression of human tumors. The reduced expression of TGF-β receptors may be an important event during cancer progression because resistance to the growth-inhibitory effect of TGF-βI will likely enable overexpression of TGF-βI hence disease progression. This reduction in expression of TGF-βRI was correlated with disease progression (14), and that overexpression of TGF-βI was closely correlated with reduced expression of both receptors (16). While moderate immunostaining reaction being the most frequent score among benign prostatic hyperplasia patients (82.6%).

Our results showed that there was an inverse correlation between TGF-βRI and TGF-βRII immunoexpression in poorly and moderately differentiated malignancy group,explained by the fact that say overexpression of TGF-βI was closely correlated with reduced expression of both receptors in human prostate cancer (16).

TGF-βRII protein was expressed in prostate tissues,with moderate immunostaining reaction being the most frequent score among benign prostatic hyperplasia patients (65.2%),and weak immunostaining reaction being the most frequent score among moderately differentiated malignancy patients (72.0%). But In poorly differentiated malignancy, negative immunostaining reaction was the most frequent score (62.5%).Also the results showed that there was significant difference in mean

level of TGF-βRII protein expression between each of poorly differentiated malignancy, moderately differentiated malignancy with P-value of 0.001,this might be due to the genetic alteration of the receptor or altered regulation of transcription that may negatively influence the stability or function of the protein (17). This was in agreement with (18), who concluded that loss of TGF-βRII immunoreactivity correlates with the aggressiveness of prostate cancer as determined by Gleason score and therefor with disease progression.

Our results showed that there was direct association betweenTGF-βRI and TGF-βRII immunoexpression in poorly and moderately differentiated malignancy group,with P value of =0.0001. This may be due to that TGF-β signaling is initiated by the binding of TGF-β ligands to type II TGF-β receptors (TGFβRII).Once TGF-β bound, TGF-βRII recruits and phosphorylates the type I TGF-β receptor (TGF-βRI), which stimulates TGF-βRI protein kinase activity(19). Activated TGF-βRI then phosphorylates two downstream transcription factors SMAD2 and SMAD3, allowing them to bind to SMAD4. The resulting complexes of SMAD translocate into the nucleus and interact with other transcription factors in a cell-specific manner to regulate the transcription of a multitude of TGF-β-responsive genes (20, 21). In conclusion, reduction in TGF-βR1 and TGF-βR2 expression correlate significantly with prostate cancer progression.

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تعبير مستقبلات عامل تحويل النمو (TGF-β) النوع الاول والثاني في سرطان البروستات

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3 المركز العراقي لبحوث السرطان والوراثة الطبية/ الجامعة المستنصرية

الخلاصه:

سرطان البروستات هو الورم الخبيث الاكثر شيوعا والسبب الرئيسي الثاني لوفيات السرطان ذات الصلة بين الذكور. سرطان البروستات ينشأ في البروستات, الغدة التي تقع تحت المثانة وفقط امام المستقيم . الالتهاب هوعملية فسيولوجية جوهرية والتي يمكن ان تنشأ في أي نسيج استجابة الى ضرر الصدمات وضرر الاصابات والضرر المتسبب بواسطة المناعة الذاتية . عامل تحويل النمو بيتا 1(TGF-β1) هو المنظم المحتمل لنمو الخلايا السرطانية في البروستات والذي يبعث إشارات من خلال معقد متباين مؤلف من النوع 1 والنوع 2 من المستقبلات .أجريت هذه الدراسة لتحديد العلاقة بين التعبير عن عامل تحويل النمو بيتا 1(TGF-β1) ,المستقبل الاول لعامل تحويل النمو بيتا (TGF-βR1),المستقبل الثاني لعامل تحويل النمو بيتا (TGF-βR2) و تطور سرطان البروستات. وكذلك لتحديد دور الانترلوكين17 في تطور سرطان البروستات. تم استخدام تقنية التعبير المناعي النسيجي الكيميائي (IHC) في الكشف عن مستوى التعبير عن عامل تحويل النمو بيتا 1(TGF-β1) , المستقبل الاول لعامل تحويل النمو بيتا (TGF-βR1), المستقبل الثاني لعامل تحويل النمو بيتا (TGF-βR2) بروتين في انسجة مرضى سرطان البروستات ومجموعة السيطرة. تم استخدام تقنية التعبير المناعي النسيجي الكيميائي (IHC) ايضا لدراسة تعبير المستقبل الاول لعامل تحويل النمو بيتا (TGF-βR1) في نسيج البروستات . أظهرت النتائج بأن هذا البروتين تم تعبيره في 3 (18.7%) و 14 (56%) من الورم الخبيث ضعيف و متوسط التمايز على التعاقب, مع تفاعل ضعيف للصبغة المناعية هي النتيجة الاكثر شيوعا. كان هنالك اختلاف واضح بمعدل مستوى تعبير بروتين المستقبل الاول لعامل تحويل النمو بيتا بين كل المجاميع المدروسة. المستقبل الثاني لعامل تحويل النمو بيتا (TGF-βR2) هو بروتين تم تعبيره في 6 (37.5%) و 22 (88%) من الورم الخبيث ضعيف و متوسط التمايز على التعاقب, مع تفاعل ضعيف للصبغة المناعية هي النتيجة الاكثر شيوعا. كان هنالك اختلاف واضح بمعدل مستوى تعبير بروتين المستقبل الثاني لعامل تحويل النمو بيتا (TGF-βR2) بين كل المجاميع المدروسة.