PUBLICATIONS AND PRESENTATIONS

Publications related to the thesis:

1. **Research Article: Gaurav Chauhan**, Avani Mehta, Sarita Gupta; Stromal-AR influences the growth of epithelial cells in the development of Benign Prostate Hyperplasia (June 2020). Molecular and Cellular Biochemistry (2020), Springer https://doi.org/10.1007/s11010-020-03773-z (Online) IF: 2.9

2. **Review Article: Gaurav Chauhan**, Ragitha Chruvattil, Akhilesh Prajapati, Abhishek Pethe, Krishma Taylor, Bernard Kwabi Addo, Sarita Gupta; Intricacies of Androgen Receptor in dynamics of prostate cancer stem cells (2020). Under Submission.

3. **Research Article: Gaurav Chauhan, Abhishek Pethe, Steffi Verghese, Akhilesh Prajapati, Sarita Gupta;** AR targets LGR4 and NP63 through β-Catenin for stem cell regulation in benign prostate tumors. (Under Preparation)

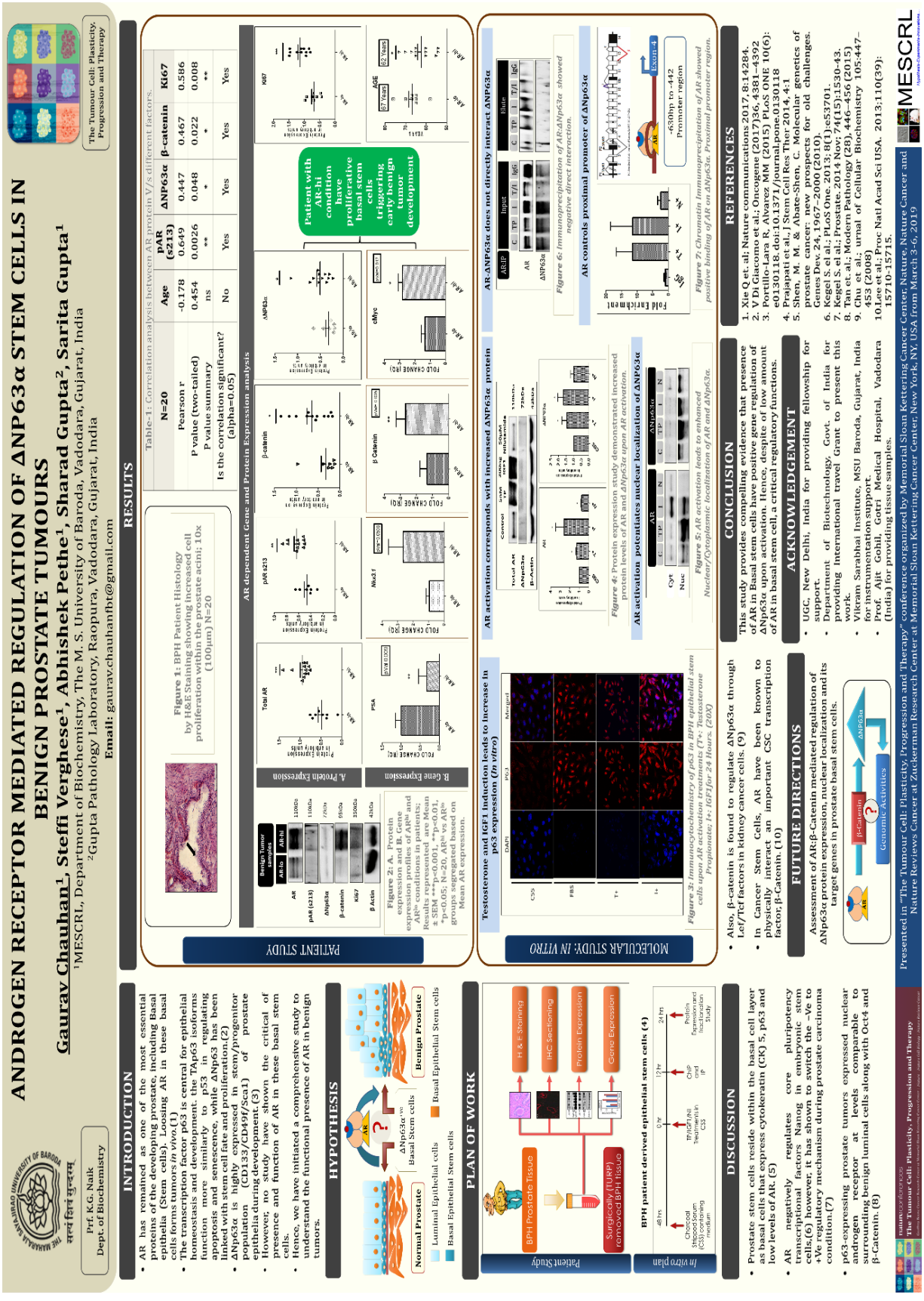
Other publications:

1. Manit Gandhi, Priyanka Bhatt, **Gaurav Chauhan**, Sarita Gupta, Ambikanandan Misra, Rajashree Mashru (2019). IGF-II-Conjugated Nanocarrier for Brain-Targeted Delivery of p11 Gene for Depression. AAPS PharmSciTech, 20(2), 50. doi: 10.1208/s12249-018-1206-x.

2. Prachi D. Karia, Laxmi A. Patil, Mitul S. Vakani, **Gaurav Chauhan**, Sarita S. Gupta, S. P. Rathod, Kirti V. Patel (2019). Chemoprevention of breast cancer by Psidium guajava Linn. Asian Journal of Pharmacy and Pharmacology 2019; 5(1):58- 68. doi:10.31024/ajpp.2019.5.1.8.

3. Akhilesh Prajapati, **Gaurav Chauhan**, Sharad Gupta, Parth Pandya, Sukhbir Kaur and Sarita Gupta; Analysis of AR, PSA (KLK) and ER-β Genetic Variants and Benign Prostate Hyperplasia (BPH) Pathogenesis in Indian Population. Biomedical Research Journal; 2016; 3(1):88–103. doi: 10.4103/2349-3666.240607

Presented articles as posters



ANDROGEN RECEPTOR INTERVENES THE EXPRESSION OF LGR4 THROUGH miR-27A IN BENIGN PROSTATE TUMOR

Gaurav Chauhan[1], Abhishek Pethe[1], Sharad Gupta[2], Sarita Gupta[1]

[1]Department of Biochemistry, The M. S. University of Baroda, Vadodara, Gujarat, India

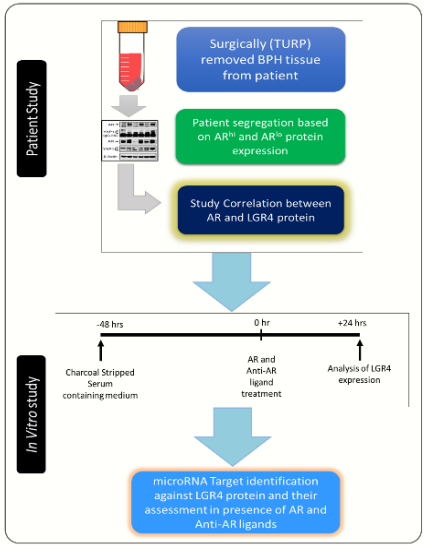
[2]Gupta Pathology Laboratory, Raopura, Vadodara, Gujarat, India

INTRODUCTION

- Benign Prostate Hyperplasia (BPH) causes two to three-fold increased risk of Prostate cancer (PCa) incidence with a two to eight-fold increased risk of PCa mortality.[1]
- Both BPH and PCa are driven by Androgen Receptor (AR) that holds the key regulatory network in prostate diseases.
- Recently, investigation by Xie et al showed presence of AR in both basal and luminal progenitor stem cell populations.[2] Leucine Rich G-Protein Coupled Receptor 4 (LGR4) is such an epithelial basal stem cell marker, and has been identified as one of the markers of Prostate CSCs and has been shown to be a key regulator of prostate development.[3]
- Our preliminary data of BPH epithelial cells showed co-existence of AR and stem cell markers including LGR4. Moreover, protein profiling of BPH patient tissue samples also showed similar pattern. However, no study elucidates co-existence of AR and LGR4 in benign tumors.

OBJECTIVE & WORKPLAN

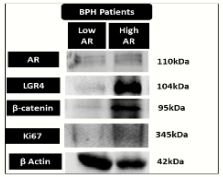
We aim to understand the role of AR in regulation of LGR4 in Benign tumors.



RESULTS

AR dependent evaluation of BPH Patient tissues

N=20	AR	β-Catenin	LGR4	ki67
Pearson r	0.6162	0.5667	0.4725	0.5077
P value (two-tailed)	0.0019	0.0114	0.0177	0.0132
P value summary	**	*	*	*
Significant correlation? (alpha=0.05)	Yes	Yes	Yes	Yes



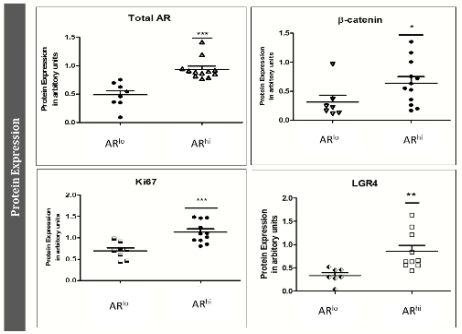


*Figure 1: a) Gene expression of AR driven genes in patients with AR^hi and AR^lo. b) Protein expression of Total AR, pARs213, Ki67 and Lgr4 in patients with AR^lo (n=12) and AR^hi (n=8); **p<0.01, ***p<0.001; AR^lo V/s AR^hi; Mean±SEM*

Testosterone induction leads to increase in LGR4 protein expression (*In vitro*) in BPH epithelial cells

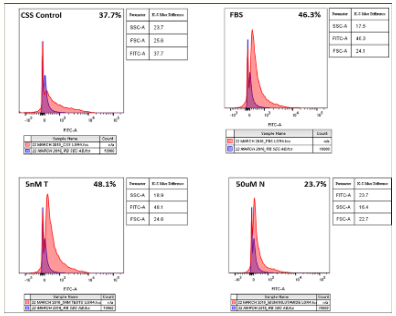


Figure 2: Flowcytometric analysis of LGR4 in BPH cells post-treatment of SnM Testosterone Propionate (AR activator) and 50μM Nilutamide (AR inhibitor)

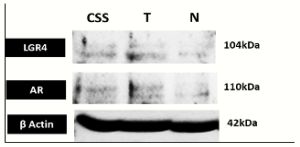


Figure 3: Western Blot analysis of LGR4 and AR expression upon Testosterone and Nilutamide treatment.

Gene expression pattern of LGR4 upon Androgen/Anti-Androgen treatment

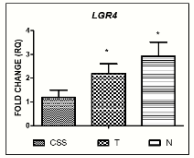


*Figure 4: Gene Expression analysis of LGR4 post Androgen/Antiandrogen treatment for 24 hours. Mean±SD; n=3 (CSS V/s treated groups); *p<0.05*

LGR4 targeting miRNA Prediction and expression

Sr. No.	Target Genes	miR	Status	Prediction Tools
1	LGR4	hsa-let-7f-5p	Predicted	TargetSCAN, Mirbase
2	LGR4	hsa-mir-34b-5p	Validated	TargetSCAN, Exiqon, Mirbase
3	LGR4	hsa-miR-27a-3p	Validated	TargetSCAN, Mirbase
4	LGR4	hsa-miR-186-3p	Predicted	TargetSCAN, Mirbase
5	LGR4	hsa-mir-34a-5p	Validated	TargetSCAN, Exiqon, Mirbase
6	LGR4	hsa-mir-34c-5p	Predicted	TargetSCAN, Mirbase

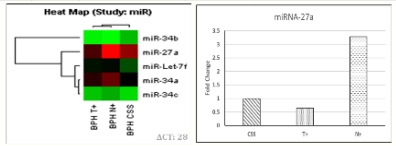


Figure 5: Assessment of miR-27a expression upon Testosterone and Nilutamide treatment for 24 hours. (CSS V/s treated groups)

DISCUSSION

- Patient study suggests that AR is directly correlated with LGR4 expression in benign tumors. Also, AR^hi patients have increased expression of Ki67 and LGR4 proteins suggesting hyperproliferative condition.[4]
- AR/ β-Catenin interaction is known as a direct effector of Wnt signaling and LGR4 also potentiates Wnt/β-Catenin signaling.[5] It has been observed that miR27a is the modulator of Wnt/β-Catenin signaling in oral carcinoma stem cells.[6] It has been observed that miR-27a was also found to be androgen-regulated. However, miR-27a is known as onco-mir and highly expressed during PCa.[7]
- Results signifies of AR/LGR4 to activate Wnt signaling and potentiate stem cell proliferation in these cells via suppressing .

CONCLUSION

The study provides a compelling evidence that AR is directly correlated with LGR4 expression during benign tumors. Activation of AR suppresses miR27a expression that increases LGR4 protein translation.

ACKNOWLEDGEMENT

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Gotri Medical College for providing patient samples

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Hypothesis-Experiments-Innovations...

Unraveling the potentials of novel therapy for Benign Prostate Hyperplasia and Prostate Cancer: An *in vitro* study

Gaurav Chauhan, Dievya Gohil, Akhilesh Prajapati, Sarita Gupta*

Department of Biochemistry, Faculty of Science, The Maharaja Sayajirao University of Baroda,Vadodara, Gujarat 390002, India.

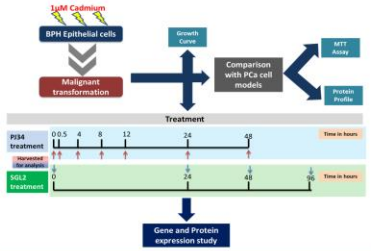
ABSTRACT

Prostate associated pathologies Benign Prostate Hyperplasia (BPH) and Prostate Cancer (PCa) both are widely studied but still reports relating their association with each other as well as their treatments are very scanty. To understand the disease progression of BPH to PCa, BPH cells developed from Human BPH tissues were exposed to Cadmium, a potent carcinogen in *in vitro* condition and were found to be transformed to cancerous phenotype. In these diseases, one of the key markers that differentiate BPH and PCa is loss of p63 protein in PCa condition. p63, a tumor suppressor and homologue of p53, expresses in prostatic stem cells and regulates apoptosis in these cells. The results demonstrated that there was down regulation of p63 protein expression when BPH cells were exposed to Cadmium depicting cancer like condition. Additionally, in PCa condition, Poly-ADP Ribose Polymerase (PARP) activity, associated with apoptosis and DNA repair, is up regulated however; the expression of cleaved PARP and caspase is less as compared to BPH. Further, we attempted to treat BPH, Transformed BPH cells and PCa (PC3) cells with PARP inhibitor (PJ34) and a novel herbal compound SGL2 isolated from *Enicostemma littorale*. The treatment with these compounds leads to recovery of p63 protein and increased PARP cleavage/Caspase3 activation implicating activation of apoptosis cascade in BPH, Transformed and PCa cells by SGL2 but transformed cells showed resistance against PJ34 treatment. Thus, the current study demonstrates that SGL2 implicate better anti-cancer activity than PJ34.

INTRODUCTION

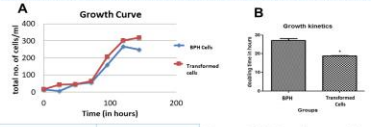
Benign prostate hyperplasia (BPH) and prostate cancer (PCa) are two major complications for surgical interventions in men. Additionally Pca is the second most prevailing cancer in western world. There are several common aetiologies, like Hormonal, Genetic and environmental factors, associated with both the diseases. One of the factor that contributes to both of these pathogenesis is Cadmium (Cd). A study in our lab suggests that Cd exposure can induce carcinogenesis in benign epithelial cells. After exposure to Cd-acetate (1µM), benign epithelial cells showed cancer phenotype and metastasis. This change also modulates cancer stem cells and showed similar expression profile in PCa. One of the major concern today is the many therapeutic interventions like chemotherapy, hormone receptor modulators, surgery, and herbal therapies are available for prostatic diseases. Presently, PARP inhibitors are under clinical evaluation for their therapeutic potential as anticancer agents. Currently, phytochemicals have emerged as a potential anticancer agents due to their prophylactic, anti-oxidant, anti-inflammatory and immunomodulatory action. In this context, we evaluated PARP inhibitor (PJ34) and SGL2, a phytochemical derived from *Enicostemma littorale*, for their anticancer effect on transformed cells and cancer cell lines LNCaP and PC3. One of the key events of apoptosis is p63 activation, caspase-3 and PARP cleavage in prostate cells.

PLAN OF WORK



RESULTS

Growth Kinetics after 1µM Cadmium Acetate Treatment



Cell Type	Doubling Time
BPH cells	27.06 ± 1.055 hours
Transformed cells	**18.81 ± 0.235 hours**

Figure 1:(A) Growth curve of BPH and Transformed cells **(B)** Doubling time of BPH and Transformed cells

Observations± SEM, *p< 0.05 BPH v/s Transformed cells

Protein expression profile of BPH, Transformed and PCa Cell-lines

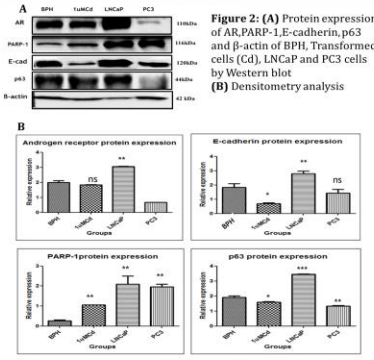


Figure 2: (A) Protein expression of AR,PARP-1,E-cadherin, p63 and β-actin of BPH, Transformed cells (Cd), LNCaP and PC3 cells by Western blot
(B) Densitometry analysis

Results represent mean of three observation ± SEM ***p<0.001, **p<0.01, Control vs. Transformed, LNCaP and PC3 cells.

Dose Standardization by PARylation for treatment of PARP inhibitor (PJ34)

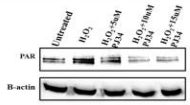


Figure 3: Image showing PAR expression in BPH cells

MTT Assay for PJ34 and SGL2

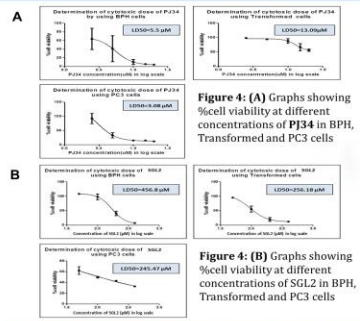


Figure 4: (A) Graphs showing %cell viability at different concentrations of **PJ34** in BPH, Transformed and PC3 cells

Figure 4: (B) Graphs showing %cell viability at different concentrations of SGL2 in BPH, Transformed and PC3 cells

Time dependent treatment of PJ34 and SGL2 on BPH, Transformed and PCa Cell-lines

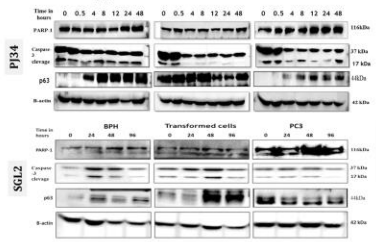


Figure 5: Images showing expression of PARP-1, Caspase -3, Activated Caspase3, p63 and β-actin in BPH, Transformed and PC3 cells after PJ34 and SGL2 treatment.

SGL2 modulate stem cells in cancer

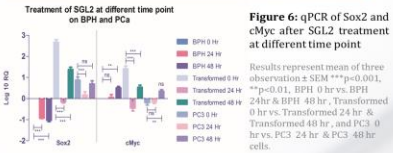


Figure 6: qPCR of Sox2 and cMyc after SGL2 treatment at different time point

Results represent mean of three observation ± SEM ***p<0.001, **p<0.01, BPH 0 hr vs. BPH 24hr & BPH 48 hr , Transformed 0 hr vs. Transformed 24 hr & Transformed 48 hr , and PC3 0 hr vs. PC3 24 hr & PC3 48 hr cells.

DISCUSSION

- Cancer cells are characterized by 2-25 times increased growth rate and proliferation then the normal cells.[5] Growth kinetics of Transformed cells showed increase in growth rate as compared to that of BPH cells after 8 week of 1µM Cd treatment .
- Higher expression of AR, PARP-1 in cancer conditions then in benign conditions,[7][2] human prostate carcinomas have correlated the loss of E-cadherin to tumor cell invasion and metastasis[1] and Loss of expression of tumor suppressor protein p63 has been associated with high grade PCa.[4]
- caspase-3 activation and PARP cleavage: Reduced caspase-3 cleavage in transformed cells as well as complete absence of PARP cleavage indicated apoptotic resistance of transformed cells to treatment with PARP inhibitor. [3]
- p63 is known to induce cell cycle arrest and apoptosis in human cancer cells[6] Expression of p63 increased in all groups after PARP inhibitor and SGL2 treatment implying p63 mediated initiation of cell death.
- p63 also regulates gene expression of cMyc to drive keratinocyte proliferation and differentiation.[8]

CONCLUSION

This study provides compelling evidence that Cd induced carcinogenesis could be treated with SGL2 where it showed resistance to PARP inhibitor. Moreover, this study highlights that plant compound also has potential to modulate Cancer stem cells. So, further insights to understand anti-cancer potential and ability to modulate cancer stem cell of SGL2 will be helpful to unravel new molecular targets for cancer therapy.

ACKNOWLEDGEMENT

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The Gujarat Cancer & Research Institute, Ahmedabad on 5th February, 2016**

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Hypothesis-Experiments-Innovations...

Association of Single Nucleotide Polymorphic candidate genes with Benign Prostatic Hyperplasia in western part of Indian population: A genomic approach

Akhilesh Prajapati[1], **Gaurav Chauhan[1]**, Sharad Gupta[2], Sarita Gupta[1]*

[1] Department of Biochemistry, Faculty of Science, The Maharaja Sayajirao University of Baroda,Vadodara, Gujarat 390002, India. ,

[2] Gupta Pathological laboratory,Vadodara, Gujarat, India.

ABSTRACT

Benign Prostate Hyperplasia (BPH) disease pathogenesis is still an enigmatic problem and there are no well established biochemical or genetic markers for diagnosis. Single Nucleotide Polymorphisms (SNPs) are considered very promising genetic markers for a better understanding of the genetic basis for various complex diseases. So in light of that, we investigated the susceptibility of SNP in candidate genes (Androgen receptor (AR), Prostate Specific Antigen (PSA)) with BPH risk in western part of Indian population emphasizing on smoking habits. Total 200 BPH subjects were studied with proper inclusion and exclusion criteria. The Association study between SNP and higher percentage smoking habit further strengthen the fact. SNP data was further correlated with mRNA expression profile of the respective genes. Interestingly, we found significant increase in protein and gene expression of AR with A/G genotype and increase PSA gene expression in A/G genotype.

In conclusion, the association of BPH pathogenesis and its severity can be due to the alteration in multiple candidate genes, which leads to the pathology of the prostate gland at transcriptional and translational level.

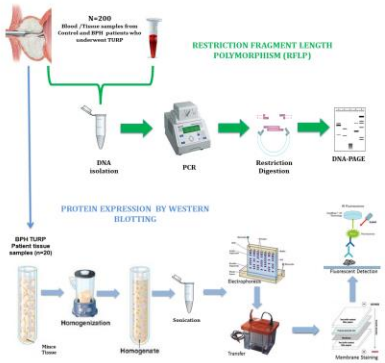
INTRODUCTION

Benign prostate hyperplasia (BPH) and prostate cancer (PCa) are two major complications for surgical interventions in men. There are several common aetiologies, like Hormonal, Genetic and environmental factors, associated with both the diseases. Identifying the environmental factors that may modify the relationship between genetic polymorphisms and disease may provide a clue to possible functions of the genetic polymorphisms or to the locations of functional SNPs. Androgen receptor (AR) polymorphisms for pathogenesis of BPH and their association have been reported (Konwar et al. 2008). Polymorphisms in AR have also been linked to PSA production (Xu et al. 2002) and also the risk was AR CAG allele repeats (Xue et al. 2000). It was also found that men carrying two copies of the PSA G allele had nearly three folds increased risk of prostate cancer. Moreover, the risk was more elevated among men who also carried a short AR CAG alleles (Xue et al. 2000). So in light of that, we aimed to investigate the susceptibility of polymorphism in candidate genes (AR & PSA) with BPH risk and genotype-phenotype correlation studies including smoking habit in 200 BPH patients including controls.

Prostatic Gene Name & Ref. Seq. No.	Polymorphism
Androgen Receptor (AR) **RS6152**	A/G at position 1754 on Exon-1
Prostate specific antigen (PSA) **RS266882**	A/G at position -158 on Promoter region

Polymorphisms studied in the study

MATERIALS & METHODS



RESULTS

AR	Observed genotype count		Expected genotype count		Chi sq. test χ^2	p value for HWE	p value
	A/A	A/G	A/A	A/G			
Control (n=119)	84	35	85.68	88.06	32.0	0.06	0.0002 ***
Patients (n=79)	35	44	41.08	71.1	11.23	0.006	

*Association studies for the androgen receptor (AR) gene A/G polymorphism at position 1754 in exon-1in BPH patients and controls (***p<0.05)*

PSA	Observed genotype count			Expected genotype count			Chi sq. test χ^2	P value for HWE	p value
	A/A	A/G	G/G	A/A	A/G	G/G			
Control (n=120)	50	54	16	49.45	55.44	15.6	0.056	0.81	0.08 (ns)
Patients (n=76)	20	41	15	21.36	38	16.8	0.54	0.46	

Association studies for the Prostate Specific Antigen (PSA) gene A/G polymorphism at ARE1 of PSA Promoter -158 A/G in BPH patients and controls. (p>0.05, ns-Non-significant)

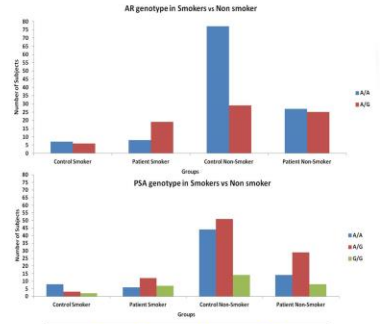
The data were represented using Hardy Weinberg Equilibrium (HWE) and λ^2 Test using Graph Pad prism v5.0 software.

(p-Values < 0.05 considered as statistically significant)

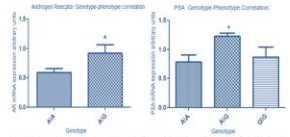
Gene	No. of Controls (%)	No. of Patients (%)	Odd Ratio (95% CI)
AR genotype			
A/A(418bp)	84 (70.6)	35(44.3)	OR 3.0 ; (95% CI 1.67-5.46) p Value=0.0002 ***
A/G(329/89bp)	35 (29.4)	44(55.7)	
Total	119(100)	79(100)	
PSA genotype			
A/A(300bp)	50(41.7)	20(26.3)	OR 2.0; (95% CI 1.07-3.74)
A/G(150/300bp)	54(45.0)	41(54.0)	
G/G(150bp)	16(13.3)	15(19.7)	
Total	120(100)	76(100)	

*Distribution of AR and PSA Genotypes among cases and controls (***p<0.05)*

Genotype correlation of smokers v/s non-smokers

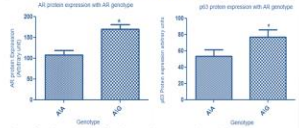


Gene Expression profile



*Genotype Phenotype correlation of AR (*p<0.05, A/G vs A/A) & PSA(*p<0.05, A/G vs A/A)*

Protein Expression profile



*Correlation of AR and p63 protein expression with AR genotype. (*p<0.05, A/G vs A/A)*

DISCUSSION

- In the study, A/G genotype frequency of AR was found to be 55.7% (OR 3.0 (95% CI 1.67-5.46) showing 3 fold increase in BPH risk whereas, A/G genotype frequency of PSA was 54 % (OR 2.0, 95% CI 1.07-3.74) in BPH patients respectively.
- A/G genotype of AR gene was more in smoker patients as compare to smoker control subjects, whereas A/A genotype had been observed in control population. Similarly, A/G genotype of PSA gene found to be more in smoker patients compared with smoker control population and the same was found in Non-smoker individuals.
- Increased protein expression of p63 had been observed with A/G genotype of AR in patients compared to A/A, indicating hyperplasia condition and role of AR in pathogenesis of BPH.
- Polymorphisms in AR have been linked to differences in rates of PSA production (Xu et al. 2002) and the risk was more elevated among men who also carried a short AR CAG alleles (Xue et al. 2000).
- Yu et al demonstrated AR dependant expression of p63 in ARKO mice(Yu et al, 2011).
- A recent report on AR gene polymorphism (rs6152) in BPH also strengthen our data (Kucerova et al, 2014).

CONCLUSION

In conclusion, the association of polymorphism in BPH pathogenesis and severity can be due to the alteration in multiple prostate genes which leads to the pathology of the prostate gland at transcriptional and translational level. Further this study can be used to design personalised medicine for future therapeutics for BPH pathogenesis.

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