

CHAPTER-2

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AIMS AND OBJECTIVES

2.1 Rationale of the study

Human empowerment is insidious to the existing life on the earth. Industrialization, urbanization and modernization have extensively impacted the life of the people. Many pesticides, recalcitrant compounds and environmental pollutants ingested in any form are accumulated over a period of time and are responsible for various clinical manifestations.

A very common pathology in the aging human male is the abnormal growth of the prostate gland, as reflected in the incidence of benign prostatic hyperplasia (BPH) and prostatic cancer (PCa). Despite the magnitude of morbidity and mortality associated with these diseases, very little is known regarding the mechanisms involved in prostate tumorigenesis. A variety of growth factors, steroidal hormones, stem cells and other factors are involved in normal prostatic morphogenesis and function, but their role in BPH and PCa remains poorly understood. BPH and PCa are multi-factorial diseases associated with androgen, estrogen, hereditary and environmental factors. Disease pathogenesis is very vague and there is no well established biochemical and genetic markers for early detection, which can differentially diagnose PCa and BPH. However, PSA is using as a diagnostic marker but it is not sufficiently reliable to determine the clinical stage on an individual basis (Oesterling et al 1991).

There is an association of environmental pollutant and old age male wherein cadmium, a heavy metal commonly found in the environment might lead to enlargement of the prostate gland and alters various reproductive and other urethral functions. Cadmium is a major constituent of cigarettes and bidis hence, smokers are the major sufferers of this disease. Cadmium is known for androgenic and estrogenic mimicking activity and the metal has high affinity to bind with steroid hormone receptors which might play important role in prostate enlargement.

There are limited sources that provide detailed insights of BPH pathogenesis hence, it is evidently very important to have precise and informative study models. To date there are few models that elucidate mechanisms involved in the pathogenesis of BPH. However, there is no convenient, economically viable and BPH mimicking model, which makes an urge for

developing a best suitable model that would help in establishment, progression and pathogenesis of this disease.

Cellular compartment of prostate plays a major role in functioning of this organ. Stromal and epithelial cells are responsible for development of BPH. Epithelium of prostate is a very good niche for stem cells. However, there is a big lacuna regarding the status of the stem cells present in BPH condition. Hence, it is important to unlock several mysteries of the prostatic stem cells in BPH. Also there was an urge how androgen and estrogen are related to BPH. As cadmium mimics androgen and estrogen receptor mediated action, it creates curiosity to understand the interplay and crosstalk between cadmium, the hormones and the prostatic stem cells which would resolve the hidden facts of BPH pathology and understand if any correlation exists between BPH and PCa.

According to epidemiological studies Asian population is profoundly associated with BPH whereas, the western part of the world is more associated with PCa. This might be due to genetic polymorphisms. To date several functional and non-functional genetic polymorphisms have been reported to have positive association with prostatic growth, but genetic polymorphisms associated with BPH are yet to be investigated. Positive associations of these SNPs with prostatic growth entail us to identify the putative biomarkers associated with BPH.

2.2 Aim of the Study

The present study was proposed to understand the etiopathogenesis of BPH in Indian population with respect to altered genetic and cellular functions. This study was designed with three different aspects, first one is focused on establishment of BPH animal model, second to study cellular status in prostatic tissue obtained from BPH patients who underwent TURP (Trans Urethral Resection of Prostate) surgery. Further, third aspect of the study is to understand the genetic association of novel SNP in Indian population would be used as marker in early diagnosis of BPH and to differentiate from PCa.

Thus, this study was designed to unravel the plethora of risk factors associated with mystery of this disease. Development of a rodent model, understanding the cellular pathogenesis and to elucidate the biomarkers associated with this disease is the major aim with the following objectives of current study.

2.3 Objectives

Objective-1: Establishment of BPH rat model & validation of progression of diseased condition in *in-vivo* model.

Objective-2: Isolation of epithelial & stromal cells from Benign Prostate Hyperplasia patient's.

- a. Analysis of cellular and molecular status of both cell types and to understand the role of stem cell in benign prostate hyperplasia tissue.
- b. To study the link between BPH and PCa by using Human BPH epithelial cell-line using Cadmium as model.

Objective-3: To understand the genetic association of single nucleotide polymorphism in human prostate genes from benign prostate hyperplasia patients.