# CHAPTER-2

## 2. AIMS AND OBJECTIVES

### 2.1 Rationale of the study

The role of androgens has been well defined in prostate growth and function during the adult age of the men. The androgens exert their actions via activation of AR that acts as a transcriptional factor (TF) in the prostate cells. AR function depends upon its posttranslational modifications, total protein levels, and structural stability. Thus, AR signaling has been the central player for maintaining the tissue homeostasis in the prostate gland. As a TF, AR interacts with specific coregulators and binds to the ARE sequences on the DNA to control the expression of target genes and secretions from the luminal cells. Further, the activity of AR can be modulated by several cell signaling proteins and other TFs providing a balanced interaction of AR with androgen and other growth factors.

An increase in prostate size, inflammation, metabolic changes, activation of embryonic signaling and androgens/AR signaling play a substantial role in the development of BPH and PCa. DHT stimulated AR supports the proliferation and survival of the cells in the BPH and PCa conditions. In elderly men, despite the decreased serum testosterone levels, AR signaling is more pronounced within the tissue due to its consistent activation via stromal factors. Furthermore, androgen-independent activation of AR primarily acts via Serine213 phosphorylation and many truncated variants, like ARV7, which is the most transcriptionally active, Ligand-binding domain truncated variant of AR. Due to enhanced protein-protein interactions and gene regulatory actions through full-length or half ARE sites, its role becomes complex in the cells during BPH and PCa conditions. Hence, AR is elucidated as the vital component of BPH and PCa development, and thus its regulatory roles have been widely studied in prostate pathologies.

In addition to AR, alterations in stem/progenitor populations also became more evident during BPH and PCa development. At the cellular level, AR is expressed at different concentrations in BSCs, luminal progenitors, secretory luminal cells, and smooth muscle cells in the prostate gland. Furthermore, hyperactivation of AR signaling in the stem/progenitor and luminal cells lays the foundation for tumor cell proliferation during PCa occurrence. Our previous investigations showed the presence of AR and stem/progenitor phenotype in the BPH epithelial cells, which is lost upon the induction of

malignant changes. However, the precise role of AR in these stem/progenitor cells is not completely understood in the BPH condition. Hence, deciphering the correlation between AR and stem/progenitor cells may facilitate a better understanding of BPH pathogenesis. Additionally, assessment of the regulatory role of AR over stem-associated genes will provide new insights for understanding the vital role of AR in BPH condition.

AR expression is more abundant in epithelial cells than in stromal cells which is directly correlated with the development of BPH and PCa through increasing epithelial cell population. However, discoveries have also depicted the profound role of the AR expression in stromal cells. Decreasing stromal-AR levels has been identified as one of the vital events in prostate tumor growth and metastasis. Reports have also revealed the altered secretion profile of the stromal cells due to the loss of stromal-AR expression in PCa tumor microenvironment. During the BPH condition, the expression of stromal-AR is decreased as compared to normal conditions. However, it is not completely lost as observed in PCa tumors. Hence, the evaluation of Stromal-AR potential will shed more light to expose the mechanism of BPH pathogenesis.

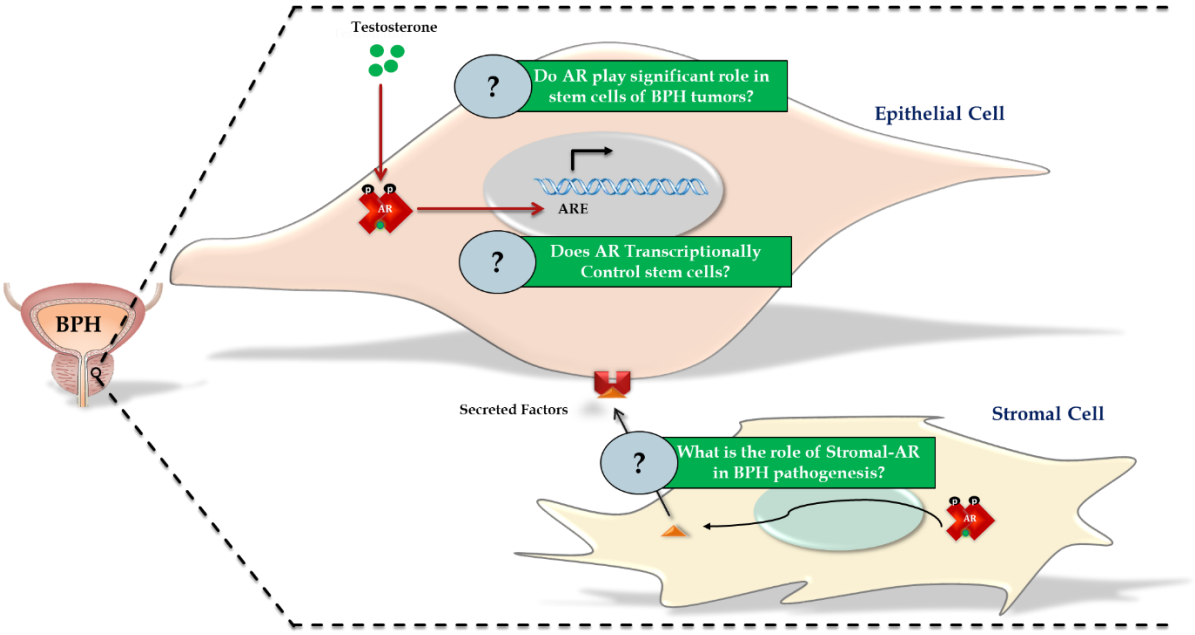


**Figure 2. 1:** Schematic representation of the hypothesis of the present study.

In light of the literature and our earlier lab reports, we aim to understand the role of epithelial and stromal AR in stem cell regulation and BPH pathogenesis by undertaking the following objectives.

## 2.2 Specific objectives of the study

**Objective-1: Association of Androgen Receptor and stemness in BPH and PCa patients.**

To enhance the understanding of AR in BPH and PCa development, we have monitored the expression of AR and correlated it with various stemness and signaling markers in the surgically excised (through TURP) BPH patient tissues and correlated AR expression with stemness in prostate adenocarcinoma patients from TCGA data repository The work depicted some intriguing findings and unique directions to further explore the role of AR in BPH and PCa.

**Objective-2: To elucidate the role of Androgen Receptor in the maintenance of stemness in benign prostate hyperplasia derived epithelial stem cells.**

After developing the correlation between AR and stemness markers, we aimed to explore the regulatory role of AR on stemness markers in BPH and PCa patients. Attempts have been made to understand the role of AR in the sphere-forming ability of the stem/progenitor BPH cells *in vitro*, and the interaction of AR and β-CATENIN, that controls the expression of stem/progenitor genes in BPH epithelial cells.

**Objective-3: To explore the role of Androgen Receptor-mediated epithelial-stromal crosstalk in the etiopathology of Benign Prostate Hyperplasia.**

In addition to AR expression in epithelial cells, AR expression of stromal cells also influences the disease progression significantly through its paracrine actions. To address the role of Stromal-AR, we assessed the governing effect of Stromal-AR mediated secretome on BPH epithelial cells and its role in the maintenance of stem/progenitor cells.