RESEARCH SUMMARY

Androgen Receptor (AR) plays a pivotal role in the growth and development of benign and malignant tumours. Recent discoveries have also revealed the vital role of stem/progenitor cells in the development of BPH and PCa. However, the presence of AR in stem/progenitor cells and its molecular significance is still obscure. Hence, we aimed to correlate the expression of AR with stem/progenitor markers. Molecular assessment of several patient-derived benign tumours showed a significant positive correlation between AR with LGR4, β-Catenin, Oct4 proteins, and Ki-67 cell proliferation marker. Moreover, the TGCA prostate adenocarcinoma dataset also showed a similar positive correlation with AR. Further, BPH patients with increased AR levels (AR^{hi}) have been found with increased stem/progenitor phenotype against BPH patients with lower AR levels (AR^{lo}). The patients in the AR^{hi} group showed early benign tumour onset (~62 years) with an increase in Ki67 expression as compared to patients in AR^{lo} (~67 years) group. Thus, the correlation of AR with both stem/progenitor and luminal marker confirms the significant association of AR with the luminal progenitor phenotype.

The transcriptional activity of AR regulates the growth and development of benign and malignant tumors. Recent investigations showed AR critically controls basal/ progenitor cell niche in normal and pathological conditions of prostate, despite its low expression. However, the molecular significance of AR in these stem cells is still obscure. LGR4 and ΔNP63α have been identified as important regulators of prostate BSCs and also the driver of BPH and PCa. Further, we have determined the positive association of both of these markers with AR expression in BPH tissue samples in chapter-5. Hence, we aimed to understand the regulatory role of AR over LGR4 and P63 expression. Activation of AR-enhanced its nuclear localization and euchromatin accessibility along with the protein expression of LGR4, β-Catenin, and ΔNP63α in benign epithelial stem cells. Additionally, androgen-mediated activation of AR stimulated the interaction between β-Catenin and ΔNP63α. Moreover, we have discovered AR and β-Catenin mediated regulation of LGR4 and ΔNP63α promoters upon testosterone stimulation in benign epithelial stem cells. Our study exhibited a novel mechanism of AR/β-Catenin mediated regulation of stem/progenitor cells in benign tumors. Also, increased AR expression was found to be a key factor that causes early benign tumor development with increased stem cell phenotype.

Activation of epithelial-AR signaling is identified as the major cause of hyperproliferation of the cells during benign and malignant prostate conditions. However, the contribution of stromal-AR is also precarious due to its secretory actions that contribute to the progression of benign and malignant tumors. The present study was aimed to understand the influence of Stromal-AR mediated actions on epithelial cells during BPH condition. The secretome (conditioned media-CM) was collected from AR agonist (testosterone-propionate-TP) and antagonist (Nilutamide-Nil) treated BPH patient-derived stromal cells and exposed to BPH epithelial cells. Epithelial cells exhibited increased cell proliferation with the treatment of CM derived from TP treated stromal cells (TP-CM) but did not support the clonogenic growth of BPH epithelial cells. However, CM derived from Nil treated stromal cells (Nil-CM) depicted delayed and aggressive BPH epithelial cell proliferation with increased clonogenicity of BPH epithelial cells. Further, decreased AR levels with increased cMyc transcripts and pAkt levels also validated the clonogenic transformation under the paracrine influence of inhibition of stromal-AR. Moreover, the CM of stromal-AR activation imparted positive regulation of basal/progenitor pool through LGR4, β-Catenin, and ΔNP63α expression. Hence, the present study to highlight the paracrine action of activation of AR in BPH patient-derived stromal cells restrict the disease progression and retains the basal state of BPH epithelial cells. Whereas, inhibition of stromal-AR promotes AR-independent aggressive BPH epithelial cell growth and may induce rapid disease progression.

KEY FINDINGS

- Elevated levels of AR in BPH patients vitally affect the aggressiveness of the BPH condition via enhanced cell proliferation of LPs and causing early BPH development.
- The LGR4/β-CATENIN expression is substantially correlated with AR expression in BPH and PCa patients, which could be a coercing element for the malignant divergence of the BPH condition.
- Correlation of OCT4 and ΔNP63α stem/progenitor markers were associated with AR in BPH tissue but not in PCa tissue, suggesting intrigue molecular actions of AR depending on BPH and PCa condition.
- Disease-specific expression signature of AR regulated miR-27a and miR-21 exhibited differential expression of miR-21 in BPH and PCa tissues.
- Ligand-induced AR activation and its implication in the regulation sphere formation with elevated LGR4 levels was unrevealed in the BPH stem/progenitor cells.

- Testosterone induced novel protein-protein interaction between AR-β-CATENIN and β-CATENIN-ΔNP63α was discovered in the BPH stem/progenitor cells.
- AR and β-CATENIN mediated regulation of LGR4 and ΔNP63α promoters have been revealed for the first time in BPH stem/progenitor cells.
- Testosterone induction to stromal-AR alters the secretory profile of the BPH patient-derived stromal cells, that strongly influence the expression of stem/progenitor associated LGR4 and ΔNP63α proteins in BPH epithelial cells.
- Stomal factors are substantially involved in the BPH development, where activation of stromal-AR exhibit protective effect via inducing cells death in proliferative stem/progenitor epithelial cells, whereas its inhibition causes aggressive disease progression.

RESEARCH CONCLUSIONS

Activation of AR in Luminal epithelial cells as well as Luminal Progenitor cells contributes to the regulation of BPH pregression via regulating the expression of LGR4 and NP63 isoforms during BPH conditions. Further, this activity of AR is not limited to the epithelial compartment of the prostate, but stromal-AR expression also contributes to the regulation of these proteins. In conclusion, we demonstrated that activation of epithelial-AR and loss of stromal-AR positively contributes to the BPH progression.

FUTURE DIRECTIONS

- Role of AR-V7 expression in stem/progenitor cells of the prostate and its role in the development of BPH and PCa.
- Identification of the sub-sets of the various populations in the epithelial compartment of the human prostate and degree of AR and AR-V7 expression for better therapeutic interventions.
- The functional consequence of androgen stimulated β-CATENIN/ΔNP63α interaction in stem/progenitor cells of the prostate.
- Identification of AR controlled secretory factors from stromal cells that potentially control the stem/progenitor population of the prostate gland.