CHAPTER-1
INTRODUCTION
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1. Introduction and Review Literature

The prostate is a fibromuscular exocrine gland. It is a male accessory reproductive gland which secretes a complex proteolytic solution into the urethra during ejaculation. Human prostate is a walnut shaped organ and located beneath the urinary bladder. Adult human prostate weigh around 20 grams at the age of 20.

1.1 Anatomy of Prostate Gland:

The gland surrounds the first 3 cm of the urethra (prostatic urethra) as it leaves the urinary bladder. The ejaculatory ducts enter dorsally and join the urethra within the gland either side of the prostatic utricle. The most caudal aspect of the gland, which opposes the urinary bladder, is termed the base of the gland. The walls of the prostatic urethra are highly convoluted and lined with transitional epithelium. In its resting (not distended) state, the ureter has a longitudinal ridge (the urethral crest) running the length of the gland. The majority of the ductal glands secrete into longitudinal grooves (the urethral sinuses) formed on either side of the ridge. Near the junction of the ejaculatory tubes and the urethra is a short diverticulum in the urethral crest. This is the prostatic utricle, the male vestigial remnants of the female uterus and vagina. The human prostate is a complex ductal-acinar gland, divided into three anatomical zones: peripheral, transitional and central zones, surrounded by a thick-continuous fibromuscular stroma (McNeal 1984; McNeal and Bostwick 1984; Timms et al. 1994) and covered by a thin vascularised fibrous sheath. This fibromuscular layer extends within the organ as septae, dividing the gland into ill defined lobules and functional areas. (Fig. 1.1)

There are three defined concentric layers of the secretory components of the gland. (I) The innermost comprises mucosal glands, concentrated around and secrete into the upper region of the prostatic urethra, (II) the middle or internal area contains submucosal gland, secrete via short ducts into the urethral sinuses and (III) the outer or peripheral area constitutes the majority of the gland, secretes via long ducts into the urethral sinuses. The anterior isthmus is an area of the gland ventral to the urethra, relatively free of glands and rich in fibromuscular tissues.

1.2 Histology of Prostate gland

At histological level, human prostate contains mainly two major cell types that are called epithelial and stromal cells. The stromal to epithelial ratio in normal prostate of human is 2:1.
To Understand The Etiopathogenesis of Benign Prostate Hyperplasia at Biochemical, Cellular and Molecular level.

(Bartsch et al. 1987; Timms et al. 1994). Within the acini and tubules, the epithelium forms complex folds and papillae supported by a thin highly vascularised loose connective tissue. The most part of secretory epithelium is pseudostratified which comprises tall columnar cells and basal cells supported by a fibro-elastic stroma containing randomly orientated smooth muscle bundles. The epithelium is highly variable and containing cuboidal or squamous epithelium, which is also present with transitional epithelium in the distal regions of the longer ducts. Densely packed basal nuclei are characteristic of the prostatic epithelium. The tall columnar secretory cells have an extensive basal golgi complex, apical lysosomes and secretory granules. The epithelium contains scattered neuroendocrine cells, which partly control release and expulsion of prostatic secretions during ejaculation. (Fig 1.2)

**Figure 1.1:** histology of normal prostate gland

**Figure 1.2:** Prostatic Zones: PZ= Peripheral Zone, CZ= Central Zone, TZ= Transitional Zone

**Figure 1.3:** Prostate gland cells organization and their identity markers.

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1.3 Cellular organization and their molecular markers in adult prostate

Prostatic Epithelial cell layer is composed of four differentiated cell types known as basal, secretory luminal, neuroendocrine (NE) and transit-amplifying (TA) cells that are identified by their morphology, location and distinct marker expression (Fig 1.3). The basal cells form a layer of flattened to cuboidal shaped cells above the basement membrane and express p63 (a tumor suppressor gene - p53 homolog), Bc1-2 (a pro-apoptotic factor), cluster designation (CD) 44, hepatocyte growth factor (HGF) and the high molecular weight cytokeratins (CK) 5 and 14. The expression of androgen receptor (AR) is low or undetectable in the basal cells, which makes the basal cells independent of androgens for their survival (Bonkhoff and Remberger 1993; Prins et al. 2002; Long et al. 2005). The luminal cells are the major cell type of the prostate that form a layer of columnar shaped cells above the basal layer constituting exocrine compartment that secretes prostate-specific antigen (PSA) and prostatic acid phosphatase (PAP) into lumen. They are terminally differentiated, androgen dependent, non-proliferating cells, expressing low molecular weight CK8 and 18, CD57 and p27Kip1 (a cell cycle inhibitor) (Prins et al. 2002; Long et al. 2005; De Marzo et al. 2010) along with high levels of AR. NE cells are rare cells scattered in the basal and luminal layers of the prostate. They are terminally differentiated and androgen-insensitive cells, expressing chromogranin-A, synaptophysin and neuron-specific enolase (NSF) (Bonkhoff et al. 1995; Mahapokai et al. 2000; Long et al. 2005). The NE cells also produce and secrete neuropeptides such as bombesin, calcitonin and neurotensin that are believed to support epithelial cell growth and differentiation (Abrahamsson 1999; Abate-Shen and Shen 2000; Amorino and Parsons 2004). Additionally, there is a small group of intermediate cells referred as TA cells that express both basal as well as luminal cell markers (CK5, CK8, CK 14, CK 18, AR and PSA) (Bonkhoff et al. 1994; Bonkhoff and Remberger 1996; Xue et al. 1998; Hudson et al. 2000). The epithelial layer is surrounded by a stromal layer, which forms a peripheral boundary of the prostate gland. The stromal cell layer consists of several types of cells that include smooth muscle cells (the most abundant cell type in stroma), fibroblasts and myofibroblasts. Stromal cells express mesenchymal markers like CD34, vimentin, CD44, CD117 and CD90 (Takao and Tsujimura 2008).

1.4 Prostate Gland Development in human and rodent:

In contrast to the most male accessory sex glands, which develop at embryonic stage from the Wolffian ducts (mesodermal), the gland is an endodermal structure and originates from the urogenital sinus (UGS). Although the developmental process is continuous, it can be categorized in five distinct stages involving determination, initiation or budding, branching...
morphogenesis, differentiation, and pubertal maturation (Fig. 1.4). In human, the prostate gland development begins during the second and third trimester and completed by the time of birth (Lowsley 1912; Prins 1993). Final growth and maturation occur at puberty when circulating androgen levels rise sharply. However, as testosterone levels fall during the third trimester, the gland enters a quiescent state. The quiescent state persists until puberty, when testosterone levels again increase and the epithelium proliferates, giving rise to the complex infoldings seen in the mature gland. The prostate doubles in size during this phase of development, ARs are expressed by the epithelial cells and the full secretory phenotype is established. By 45 to 50 years, testosterone levels are in decline again and the prostate undergoes a period of involution (Fig 1.5). With increasing age, atrophication of the gland may continue, though commonly, benign prostatic hypertrophy occurs.

Figure 1. 4: Prenatal to postnatal morphology and development of prostate

Figure 1. 5: Age dependant Testosterone level in human
In the mouse, the initial outgrowth of epithelial buds occurs between fetal days 16.5–17.5 (f16.5–17.5) in a 19 day gestational period (Sugimura et al. 1986), while in the rat it occurs at f18.5 in a 21 day gestation (Hayashi et al. 1991).

Prostate branching morphogenesis patterns of rat and mouse are lobes specific and coordinated by cell differentiation of epithelial and mesenchymal cell in the proximal-to-distal direction (Hayashi et al. 1991; Prins and Birch 1995; Hayward et al. 1996a; Hayward et al. 1996b). Epithelial differentiation from progenitor cells into differentiated basal and luminal cells has been documented in the rat prostate with changing patterns of cytokeratins as well as alterations in AR expression, an early marker of epithelial cell differentiation (Prins and Birch 1995; Hayward et al. 1996a). Concomitant with epithelial differentiation, the prostatic mesenchyme undergoes differentiation postnatally. As the prostate undergoes branching morphogenesis, a branched vascular bed forms in parallel with neovascularization forming within the prostatic stromal elements and capillary beds extending to the ductal basement membrane (Shabsigh et al. 1999).

1.5 Physiological function of the prostate

The main role of the prostate as a male reproductive organ is to produce prostatic fluid, which accounts for up to 30 percent of the semen volume (Fig 1.6). Sperm motility and nourishment are aided by the prostatic fluid constituents. Prostatic fluid is a thin, milky alkaline (pH 7.3-7.5) fluid containing citric acid, calcium, zinc, acid phosphatase and fibrinolysin (Donkervoort et al. 1977). Prostate specific antigen (PSA) is also a constituent found in prostatic secretion. PSA is a proteolytic enzyme which liquefies semen for the motility of the sperm to fertilize the ovum (egg) (Table-1.1). Interestingly, only human and dogs experience abnormal growth of the prostate while other mammals are spared (Partin and Rodriguez 2002).

<table>
<thead>
<tr>
<th>COMPONENT</th>
<th>SIGNIFICANCE</th>
</tr>
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<tbody>
<tr>
<td>Citric Acid</td>
<td>ATP production via the Krebs cycle for sperm motility</td>
</tr>
<tr>
<td>Proteolytic enzymes</td>
<td>Break down the clotting proteins from the seminal Vesicles</td>
</tr>
<tr>
<td>(PSA, pepsinogen, amylase, etc.)</td>
<td></td>
</tr>
<tr>
<td>Prostatic Acid phosphatase</td>
<td>Hydrolyze a broad variety of small organic phosphomonoesters under acidic conditions</td>
</tr>
<tr>
<td>Seminalplasmin</td>
<td>An antibiotic that destroys bacteria</td>
</tr>
<tr>
<td>Prostaglandins</td>
<td>Smooth Muscle contraction for sperm transport</td>
</tr>
</tbody>
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Figure 1.6: semen volume portion distribution  
Table 1.1: Composition and significance of Prostatic fluid
1.6 Prostate Endocrinology

The prostate is a hormonally regulated glandular organ whose growth accelerates at sexual maturity due to androgen action on both stromal and epithelial cells (Sugimura et al. 1986; Prins and Korach 2008). At embryonic stage the determination and initiation of prostatic development in the human and rodent fetus is entirely dependent upon androgens produced by the fetal testes. Surgical or chemical castration (i.e. anti-androgen administration) of rodents during critical periods of fetal life results in inhibition of prostate development (Price 1936; Jost 1953; Price and and Williams-Ashman 1961; Cunha 1973; Lasnitzki and Mizuno 1977). However, the extent of inhibition depends on the timing of androgen ablation relative to bud initiation. In the 1970s, it was determined that the primary androgen responsible for prostatic development is dihydrotestosterone (DHT), the reduced metabolite of testosterone (Wilson and Gloyna 1970). DHT is formed in the prostate epithelium by 5α-reductase and has been shown to have higher affinity for the AR as compared with the parent compound, testosterone (Fang et al. 1969). AR are highly expressed in the UGS mesenchyme before and during prostate morphogenesis whereas epithelial AR expression is induced after budding and branching morphogenesis (Shannon and Cunha 1983; Takeda et al. 1985; Husmann et al. 1991; Prins and Birch 1995).

Study has shown that AR induction in prostate epithelium begins as early as postnatal days 1–2 (before cytodifferentiation of the epithelium and mesenchyme) (Prins and Birch 1995), it is possible that androgen-driven epithelial signals contribute to morphogenesis of the prostate by affecting the differentiation of adjacent mesenchymal cells. It is noteworthy that AR expression does not vary along the proximal distal axis of the developing and adult prostate (Prins et al. 1992; Prins and Birch 1995), thus differential gene expression along this axis is likely driven by factors other than androgens. Other steroid hormones also play a crucial role during prostate development including estrogens and retinoids (Prins et al. 2001; Huang et al. 2004; Prins and Korach 2008). Specific steroid hormone receptors have been identified to understand the prostate morphogenesis in rat, which vary in a time and cell-specific manner (Prins et al. 2002). (Fig. 1.7)
1.6.1 Androgens

The growth and maintenance of the prostate gland for its functional and structural integrity, require the constant support of an adequate level of circulating androgens (Bruchovsky et al. 1975). The testes secrete several male sex hormones, which are collectively called androgens, including testosterone, DHT, and androstenedione.

Testosterone is formed by the interstitial cells of Leydig, which lie in between the seminiferous tubules and constitute about 20 percent of the mass of the adult testes. Testes secrete large quantities of testosterone twice during life span, first when the male infant is born and the second after the puberty stage. After secretion from the testes, about 97 percent of the testosterone becomes either loosely bound with plasma albumin or more tightly bound with a beta globulin called sex hormone binding globulin and circulates in the blood in these states for 30 minutes to several hours. By that time, the testosterone either is transferred to the tissues or is degraded into inactive products that are subsequently excreted. Much of the testosterone that becomes fixed to the tissues is converted within the tissue cells to DHT by 5α-reductase enzyme, a membrane-bound enzyme that catalyzes the irreversible conversion of testosterone to DHT, with NADPH (nicotinamide adenine dinucleotide phosphate, reduced form) as a cofactor (Chen et al. 1998), especially in certain target organs such as the prostate gland in the adult and the external genitalia of the male fetus. (Fig 1.8) The testosterone that does not bind to the receptors in tissues is rapidly converted, mainly by the liver, into androsterone and dehydroepiandrosterone (DHEA) and simultaneously conjugated as either glucuronides or sulfates. These are excreted either into the gut by way of the liver bile or into the urine through the kidneys.
DHT has more affinity for the AR other than testosterone. AR, (NR3C4) (subfamily 3, group C, member 4), is a nuclear receptor. AR is nuclear transcriptional regulator and activated upon binding of DHT or testosterone (Locke et al. 2008). The location of AR gene is Xq11-12 (X-Chromosome-qArm-11-12) (Heemers and Tindall 2007; Zhu and Kyprianou 2008) and made of 8 axons containing five AR regulatory domains (Fig 1.9).

1. **N-terminal regulatory domain (NTD) A/B (Axon-1)** - N-Terminal domain is responsible for ligand activated transcriptional activity and the constitutive activity without bound ligand (Bergerat and Ceraline 2009).

2. **DNA binding domain (DBD) (Axon-2 and 3)** - This Domain contain two zinc finger domains, which functions as a DBD/LBD binding site for receptor homodimer formation (Umesono and Evans 1989).

3. **Hinge region (Axon-4)** - It is a connecting bridge between DBD with the LBD; Also contains a ligand dependent nuclear localization signal (NLS) for AR nuclear translocation by interacting with Filamin-A (Fln A) (Claessens et al. 2008).

4. **Ligand binding domain (LBD) (Axon-5, 6)** - It interacts with AF-2 and facilitates the binding of androgens, hence represents the primary key of AR signaling (Lonergan and Tindall 2011).

5. **C-terminal domain (CTD) (Axon-7, 8)** - Its interaction with NTD causes the dimerization of AR via FxxLF motifs (Lonergan and Tindall 2011).

The interaction of each domain for nuclear import of AR is regulated by interplay between each domain of the gene. These interactions aid the nuclear targeting of AR and its homodimer formation. Once inside the nucleus, AR binds to specific recognition sequences known as Androgen Response Elements (AREs) in the promoter and enhancer regions of
target genes. The AR transcriptional complex is completed by recruitment of co-regulators, which ultimately results in modulation of gene expression (Dehm and Tindall 2006).

There are two isoforms of the AR protein, AR-A and B (Roberts et al. 2004; Guo et al. 2009; Watson et al. 2010) out of which, AR-B is the predominantly expressed in the prostate (Wilson and McPhaul 1996). In prostate, AR is located in the nuclei of luminal epithelial and stromal cells. It is absent in basal cells (Chodak et al. 1992; Pelletier 2008). Binding of androgen leads to AR-Heat shock proteins (HSP) complex formation in cytoplasm and stabilized by phospho-activation of AR (Zoubeidi et al. 2007). Later, AR dissociates from HSP, homodimerizes, translocates inside the nucleus from the cytoplasm and bind to the ARE, resulting in up or down regulation of specific gene transcription (Heemers and Tindall 2007). The process includes various chaperone proteins, undergo post-translational modifications including phosphorylation, co-activation and co-repression (Nicholson and Ricke 2011). Gene expression results in the production of PSA and other various regulatory proteins important for cellular growth and function. DHT stimulates several growth factors like epidermal growth factor (EGF), keratinocyte growth factor (KGF) insulin-like growth factors (IGFs) and transforming growth factor-β (TGF-β) (Carson and Rittmaster 2003) that drive cellular proliferation in the human prostate. More recently, the importance of DHT is recognized to be two-fold: one, to act as an androgen and two, to be metabolized into 5α-androstane-3β-17β-diol (3βAdiol), an androgen which is also a ligand for ERβ (Weihua et al. 2002; Oliveira et al. 2007) (Fig 1.10).
1.6.2 Estrogens

In addition to testosterone, small amounts of estrogens are formed in the male (about one fifth the amount in the non-pregnant female), and a reasonable quantity of estrogens can be recovered from man’s urine. The exact source of estrogens in the male is unclear, but the following are known: (1) the concentration of estrogens in the fluid of the seminiferous tubules is quite high and probably plays an important role in spermatogenesis. This estrogen is believed to be formed by the sertoli cells by converting testosterone to estradiol. (2) Much larger amounts of estrogens are formed from testosterone and androstanediol in other tissues of the body, especially the liver, probably accounting for as much as 80 percent of the total male estrogen production. Estrogens exert inhibitory and/or stimulatory effects on prostate gland. They may act by inhibiting the hypothalamic/pituitary testicular axis or directly at the
prostate through receptor mediated effect. Estrogen receptor (ER) has different subtypes, ERα and ERβ (Jin et al. 1996; Chang and Prins 1999).

ERα and ERβ genes locate on the chromosome 6 and chromosome 14 respectively, demonstrating that they are encoded by separate genes and are distinct from each other. ERα and ERβ share high amino acid homology (DNA binding domain, 95 percent; ligand binding domain, 55 percent), have the same affinity for estradiol and can heterodimerize or homodimerize to form a signaling dimeric complex. Both prostatic stroma and epithelium express ERs and estrogens, which are clearly implicated in the growth of prostate. ERβ locates primarily in the epithelium but ERα is in the stroma.

There are four mechanisms of ER signalling have been reported: I) Classical ligand-dependent II) Non-classical ligand-dependent III) Non-Genomic Ligand-dependent IV) ligand-independent (Fig. 1.11). The classical ligand-dependent mechanism of ER begins with the activation of conformational changes in ER and promoting homodimerization, followed by binding to specific DNA sequence called Estrogen response elements (EREs) and activation of transcription cofactor proteins (McKENNA and O'MALLEY 2001). Non-classical ligand-dependent: genomic target with indirect binding actions; estrogen-bound ER dimers interact with transcription factors, followed by regulations of target genes. Non-genomic ligand-dependent targeted actions through estrogen-ER complex formation and phosphorylation (P) leads to activation of transcription factors (TF) and target proteins in nucleus (Kushner et al. 2000). In ligand-independent genomic target, polypeptide growth factors, such as epidermal growth factor (EGF) and insulin-like growth factor-1 (IGF-1) etc., phosphorylates ER and modulates the expression of ER genes via various cellular pathways (Smith 1998; Kushner et al. 2000).

1.7 Prostatic disorders
There are mainly three types of pathological conditions in the prostate gland: (Fig 1.12)

1) Inflammation of the prostate gland (Prostatitis)
2) Prostate Enlargement
   a) Benign Prostatic Hyperplasia (BPH)
   b) Prostate Cancer (PCa)
1.7.1 Prostatitis:
Prostatitis is an acute or chronic bacterial infection of the gland, occasionally progressing to a debilitating illness. It is a frequently painful condition that involves inflammation of the prostate and sometimes the areas around the prostate. Clinical symptoms are dribbling, testicular pain, urethral burning etc.

Four types of Prostatitis have been identified:
- Chronic prostatitis/chronic pelvic pain syndrome
- Acute bacterial prostatitis
- Chronic bacterial prostatitis
- Asymptomatic inflammatory prostatitis

1.7.2 Prostate enlargement:
Prostate gland enlargement is a common condition in elderly men. It is also called as Benign Prostate Hyperplasia (BPH) (increase in cell number), prostatic hypertrophy (increase in cell volume) and neoplasia (abnormal growth of tissue leading to carcinoma) (Fig 1.13). Prostate gland enlargement can cause bothersome urinary symptoms such as Lower Urinary Track Symptoms (LUTS).
1.7.2.A: Benign Prostatic Hyperplasia (BPH)

BPH is a slow progressive enlargement of the prostate gland which can lead to LUTS in elderly men. It is characterized by hyper-proliferation of epithelial and stromal cells in the transition zone of the prostate gland, which can be observed histo-pathologically (Schuster and Schuster 1999) (Fig 1.14).

1.7.2.1: Epidemiology

The prevalence of BPH increases markedly with increasing age. Autopsy studies have observed a histological prevalence of 8%, 50% and 80% in the 4th, 6th and 9th decades of life, respectively (Patel and Parsons 2014). Multiple observational studies from Europe, the US and Asia have demonstrated older age to be a risk factor for BPH onset and clinical...
progression by several different metrics. Studies have also demonstrated geographic heterogeneity in prostate volume and LUTS prevalence. Significantly lower prostate volumes have been observed in men from South East Asia compared to western populations (Jin et al. 1999).

1.7.2.2: Pathophysiology

Despite of its obvious importance as a major health problem, little is known in terms of biological processes that contribute to the development of BPH. To explain the etiology behind the pathogenesis of BPH, several theories, including stem cell, hormonal imbalance, apoptosis, epithelial-mesenchymal transition, embryonic awakening and inflammation, have been proposed in recent years, all of them seem to contribute together to some extent in the pathogenesis of BPH (Schenk et al. 2011; Notara and Ahmed 2012). According to stem cell theory, the stem cell population residing in the prostate gland is increased due to abnormal proliferation and down regulated apoptosis of stem cells, which may eventually contribute to BPH pathogenesis. Earlier, it was reported by Berry et al. that stem cell population is responsible for prostate gland maintenance (Berry et al. 1986). Changes in tissue consistency and cellular hyperplasia are accompanied by down regulation of apoptotic factors and increased level of anti-apoptotic factors that decrease the rate of prostatic cell death and thus, contributing to hyper-proliferation of prostatic tissue (Zhu and Kyprianou 2008). It has been reported that stromal to epithelial ratio is altered in BPH, where the ratio increases from 2:1 in normal glands to 5:1 in BPH (Shapiro et al. 1992). Stromal hyper-proliferative activity is thought to promote the development of BPH as the existence of adult stem cells in the prostate stromal compartment is speculated to expand the stroma in response to stimuli during the pathogenesis of BPH (Cramer et al. 2003).

1.7.2.3: Role of Hormonal imbalance in BPH pathogenesis:

Androgens play an important role in normal and abnormal prostate development (Bosland 2000). Both testosterone and DHT have been shown to induce prostate adenocarcinomas in experimental rat models (Noble 1977). It is known that AR signaling plays a crucial role in BPH development, and that blockade of this signaling decreases BPH volume and can relieve lower urinary tract symptoms, but the mechanisms of AR signaling in BPH development remains unclear, and the effectiveness of current drugs for treating BPH is still limited.

Tang et al found no difference in AR expression between the peripheral zone (PZ) and the transitional zone (TZ) in BPH (Tang et al. 2007). In other studies, although nucleic AR expression was detected in both epithelial and stromal cells of hyperplastic nodules, higher
expression was detected in prostate epithelial cells than in stromal cells (Kyprianou and Davies 1986; Peters and Barrack 1987). Others found higher 5-α reductase activity in stromal cells than in epithelial cells, with AR distributed evenly between epithelial and stromal cells (Krieg et al. 1983). Importantly, the primitive BPH nodules found in the periurethral area of the TZ had higher concentrations of androgens and higher nuclear AR expression than those in other prostate regions (Izumi et al. 2013). Increased prostatic androgen levels may increase the chance for prostate enlargement. Recently, O’malley et al., 2009 succeeded in quantifying the expression of four different androgen-responsive genes—ELL associated factor 2 (EAF2, also known as U19), elongation factor, RNA polymerase II, 2 (ELL2), FK506 binding protein 5 (FKBP5), and phosphoserine aminotransferase 1 (PSAT1, also known as PSA)—in either BPH or normal tissue (O’Malley et al. 2009). They demonstrated that all of the assayed genes displayed increased expression in BPH as compared with the adjacent normal glandular tissue. Data from several mouse models with selective knockout of AR in stromal smooth-muscle cells and/or fibroblasts indicate that the AR in stromal cells can also promote BPH development.

These findings suggest that androgen may play important roles in promoting the proliferation of epithelial and stromal cells in the periurethral area of the TZ, thus leading to development of BPH with urinary obstruction. The detailed mechanisms of androgen/AR signaling need to be clarified and new therapies are needed for better treatment of BPH patients.

The prostate is also a target tissue of estrogens. Estrogens exert their effects on target cells and tissues through interaction with estrogen receptors (ERs), namely ERα and ERβ. Estrogens have been implicated as a cause of benign prostatic hyperplasia (Ho et al. 2008). Excessive estrogenization during prostatic development may contribute to the high incidence of benign prostatic hyperplasia and prostatic carcinoma currently observed in the aging male population (Santti et al. 1994). An animal model of BPH showed that estradiol exerted a synergistic effect with androgens in inducing glandular prostatic hyperplasia in castrated dogs, whereas castrated dogs treated with estradiol alone developed squamous prostate epithelial metaplasia (Ho et al. 2008). Studies also reported associations between aromatase polymorphisms and altered risks of prostatic hyperplasia (Azzouzi et al. 2002; Roberts et al. 2006). Long term treatment of adult animals with estrogen or androgen leads to prostatic neoplasia (Messina et al. 1994).

The expression of ERα and ERβ in malignant prostate tissue remains unresolved (Enmark et al. 1997; Griffiths et al. 1998). In general, ERα stimulation in the prostate results in
hyperplasia, inflammation and dysplasia (Ellem and Risbridger 2009). Induction of squamous metaplasia of the prostate depends on ERα, not ERβ (Ricke et al. 2006). Estrogens have also been postulated to mediate prostatic cancer progression via ERα, as prostatic intraepithelial neoplasia does not occur in ERαKO mice and Selective ER Modulators (SERMs) that bind and inhibit ERα prevent PCa progression in mice and men.

In mice, whose ERβ gene has been inactivated (Beta Estrogen Receptor Knockout (BERKO) mice) epithelial cells in the ventral prostate are not at G0 but are always in the cell cycle. As BERKO mice age, there is a progressive hyperplasia and at 2 years of age Prostatic intraepithelial neoplasia (PIN) lesions are present. One possible mechanism for this prostate phenotype is that ERβ is a pro-apoptotic gene and that its inactivation results in accumulation of cells normally destined for death. If this is the role for ERβ in the prostate, BERKO mice will be very useful for the in-vivo study of estrogen effects on the cell cycle and for characterization of the cellular changes which occur as epithelium progresses from hyperplasia to dysplasia and carcinoma (Dupont et al. 2000). If ERβ does have a regulatory function in the prostate, ligands for the receptor would be useful in controlling proliferative diseases of the prostate. The major estrogen in mouse ventral prostate extracts is not estradiol, but 5α-androstane-3β, 17β-diol (3βAdiol). If 3βAdiol is the ligand for ERβ in the prostate, inhibition of 5α-reductase would be expected to have adverse effects on the prostate. This may explain the apparent increase in PCa in men treated with the 5α-reductase inhibitor finasteride. ERβ is the dominant estrogen receptor in prostatic epithelium and loss of ERβ results in proliferation of prostatic epithelium. It is anticipated by several reports that ERβ ligands will have a role in controlling proliferative diseases of the prostate.

1.7.2.4: Role of stem cells in BPH pathogenesis
Prostate is, structurally and functionally, a highly complex organ composed of multiple differentiated cell types, including basal, luminal and neuroendocrine cells, along with small population of relatively undifferentiated cells generally known as “stem cells” that are endowed with self-renewal and differentiation capacities (Mahapokai et al. 2000).

As the adult prostate is relatively slow growing organ with limited cycles of cell proliferation and apoptosis, the possible existence of adult prostate stem cells (PSCs) was controversial for many years. Several investigations based on stem cell models have elegantly defined role of stem cells in cellular turnover and morphogenesis of normal prostate (Isaacs and Coffey 1989; Bonkhoff and Remberger 1996) Lin et al. showed that primary culture of prostate cells from BPH patients possessed many common stem cell markers, including CD30, CD44,
CD54, neuron-specific enolase (NSE), CD34, vascular endothelial growth factor receptor-1 (Flt-1) and stem cell factor (SCF, also known as KIT ligand or steel factor) (Cramer et al. 2003; Lin et al. 2007). Although the origin of these stem cells is not known, the CD49(+) CD54(+) NSE(+) SCF(+) cell marker profile of these cells suggest that they are in a lineage closely related to MSCs. They possessed ability to differentiate into myogenic, adipogenic, and osteogenic lineages (Cramer et al. 2003; Ceder et al. 2008).

This stromal population expressed vimentin (a mesenchymal marker), CD133, c-Kit and SCF, with expression profiles similar to those observed in the Cajal cells of gastrointestinal tract, which represent a subset of stem cell-like cells. Altered patterns of c-Kit expression have been reported in benign lesions of prostate and breast tissues (Simak et al. 2000; Kondi-Pafiti et al. 2010). It has been suggested that c-Kit regulates cell proliferation in prostate and plays a crucial role in the pathophysiology of BPH via altering the expression of JAK2 and STAT1 pathways (Imura et al. 2012).

Expression of pluripotency markers such as Oct4A, Sox2, c-Myc and Klf4 might represent a stemness specific gene signature. A very recent study have demonstrated a relatively high expression of stemness associated genes, including Oct4A, Sox2, c-Myc, Nanog, and Klf4, in BPH as compared to normal prostate tissue (Le Magnen et al. 2013). Thus, several studies have revealed the presence of stem cells that express pluripotency-associated markers and are hyper-proliferative and capable of differentiation into different cell lineages within the hyperplastic prostate tissue. The presence of these high proliferative and plastic stem cells in the BPH tissue samples suggest that BPH could occur as a result of changes in the stem cell properties that could ultimately give rise to a clonal expansion of cell populations.

1.7.2.5: Stromal – Epithelial interaction:
Prostatic epithelial proliferation, differentiation and cell death are all subjected to controlling factors derived from adjacent stromal cells (Sensibar et al. 1991; Nemeth et al. 1997). Two important growth factors, keratinocyte growth factor (KGF) and transforming growth factor-β (TGF-β), are produced by prostatic stromal cells (Li et al. 2005). Prostatic epithelial cells contain receptor proteins for these growth factors (Watson et al. 2010); KGF is growth promoting (Li et al. 2005), and TGF-β is inhibitory to these cells (Sutkowski et al. 1992). Paracrine signals originating from the adjacent prostatic stromal cells, and resulting in growth stimulation or inhibition, are thought to be the fundamental step in the sequence of events resulting in abnormal growth in the prostate. (Fig 1.15)
1.7.2.6: Hereditary and Genetic polymorphism:

Clinical BPH appears to run in families. If one or more first degree relatives are affected, an individual is at greater risk of being afflicted by the disorder (Rhodes et al. 1999). Roberts et al., described data from the Olmsted County Study, regarding the association between family history of BPH and moderate to severe LUTS in the month prior to interview (Roberts et al. 2004). Men with a first degree male relative with prostatic enlargement had a 30 percent increase in risk compared to men without such family members. The increase in risk was greatest among men with relatives diagnosed before the age of 60. Men with a positive family history were also 1.3 times more likely to have an impaired peak urinary flow rate (<15ml/sec).

Different genetic polymorphism are associated with prostatic disorders, out of which various single nucleotide polymorphism (SNP/Snips) have been found in the hormonal regulatory genes and are also found to be associated with BPH, PCa or with both. These Snips occurs at every 1000 base pair in the human genome. Reports suggest an association between AR gene polymorphisms and BPH (Roberts et al. 2004). Several polymorphisms in the PSA promoter have been reported which can influence serum levels of PSA. A recent study mentioned these SNPs as a predictive marker for BPH (Thompson et al. 1997). Similarly Cramer et al., found number of polymorphisms in the PSA gene which are associated with changes in serum PSA levels (Cramer et al. 2003). Xue et. al, has reported that GG genotype of AR with AG genotype of PSA may lead to rapid and early disease progression (Xue et al. 1998). The AG genotype frequency of PSA was found to be 55.5 % (OR 0.73, 95% CI 0.16-3.4).
1.7.2.7: Risk Factors

BPH is an age dependent pathology of elderly men. BPH does not develop in men castrated before the age of forty (Moore 1944). Apart from the steroid hormones and their receptors, several other factors also play a crucial role in prostate pathology.

1.7.2.7.a: Age:

Both androgens and estrogens stimulate prostate growth. Adipose tissue, which accumulates with age, aromatizes circulating testosterone into estrogen (Shibata et al. 2000), and it has been hypothesized that alterations in the balance between testosterone and estrogen levels in prostate tissue with age may contribute to benign prostatic hyperplasia (Shibata et al. 2000; De Nunzio et al. 2012).

Epidemiological studies reported that the prevalence of BPH rises greatly with increased age. It has been reported that 70% of US men between age of 60-69 years are diagnosed as BPH patients, however it increased to 80% in those 70 years or older age (Wei et al. 2005; Parsons 2010). Population-based studies of other research teams have also demonstrated similar trends (Lee and Jeong 2014). Literature suggests that there are strong genetic components to BPH pathogenesis (Parsons 2010). Case-control analysis of lineage individual having ≤64 years of age were found to be four to six fold higher age-specific risks of BPH surgery among all primary male relatives. Similar group of researchers have demonstrated that 50% of men undergoing surgery for BPH of ≤60 years of age had a genetic lineage (Pandya et al. 2013). Several other findings have also reported higher risk of BPH at young age with genetic lineage (Sanda et al. 1997; Pearson et al. 2003; Rohrmann et al. 2006).

1.7.2.7.b: Diet and Metabolic Factors:

Diet has been reported as a risk factor for the development of BPH. In a study where men eating red meat at least daily had a 38 percent increased BPH risk (p = 0.044) compared with vegetarians (Schenk et al. 2011). Thus, large amounts of vegetables and soy products in the diet are associated with the lower rate of BPH, as they are said to be high in phyto-oestrogens, such as genestin, that have anti-androgenic effects (Scarpa 2001). In another study done in Greece, Lagiou et. al., reported that butter and margarine may increase the risk of BPH, whereas fruit intake may reduce this risk (Lagiou et al. 1999).

Studies on BMI (Body Mass Index) have reported a positive association with prostate volume: for each 1 kg/m² increase in BMI, prostate volume increased by 0.41 cc (95% CI, 0.15 to 0.84; p=0.06). Compared with men with normal range BMI, overweight and obese
men had an increased odds of prostate enlargement (p=0.01); the risk for very obese men was particularly high (De Nunzio et al. 2012).

1.7.2.7.c: Environmental pollutants:

Constantly increasing environmental pollutants due to rapid industrialization, urbanization, use of diesel generators/diesel exhaust and through the scientific and technical advancement has stimulated interest in studying toxic substances and its effects on biological system (Gopalkrishnan 1998). Cadmium (Cd) and Lead (Pb) are well known endocrine disruptors that act as estrogenic or androgenic that disturbs the normal reproductive system (Stoica et al. 2000b; Martin et al. 2002a). International Agency for Research on Cancer (IARC) considered Cd and Pb as a potent human carcinogen which are of great interest to study their role in pathogenesis of BPH and PCa (Waalkes 2003; Bertin and Averbeck 2006). It has been reported that both BPH and PCa develops due to the DNA damage and mutations, which could arise through various reasons including environmental contaminants such as Cd and Pb exposure (Burcham 1999; Fenech and Ferguson 2001; De Bont and Van Larebeke 2004). Recently, Guzel et al., showed association of Cd and Pb to BPH development and progression through the altered pro-oxidant–antioxidant balance in blood and/or tissue of 25 patients of BPH (Guzel et al. 2012). Similarly, studies carried out with the trace metals like Cr, Mn, Fe, Ni, Zn and Cu also suggest the importance of metal ions either promoting or inhibiting prostatic disorders (Guntupalli et al. 2007). Studies from our lab also showed that Cd and Pb plays critical role in pathogenesis of BPH (Chirayu Pandya thesis 2009) (Pandya et al. 2013).

The metal binds with high affinity to the hormone-binding domain of both Androgen and Estrogen receptors, and activates them (Stoica et al. 2000a). Martin et al. 2002 reported presence of epithelial proliferation and infolding in animals treated with cadmium (Martin et al. 2002b). Similarly results from our lab with BPH patients’ data also demonstrated possible association of Cd content, smoking, maximum urinary flow rate (Qmax) and PAP level with severity of BPH (Pandya et al. 2013). Other agents like DDT, PCBs, insecticides like dieldrin, endosulfan, toxaphene are also the cause of BPH and PCa. Apart from environmental influence, cigarette smoking is also recognized as one of the strongest epidemiologic risk factor responsible for manifestation of BPH and cancer (Parsons 2010).

Several pesticides, chlorpyrifos, fonofos, coumaphos, phorate, permethrin, and butylate showed correlation with exposure and increased pathological conditions in the prostate with a familial history, suggesting gene–environment interactions (Alavanja et al. 2003; Mahajan et
al. 2006). However, extensive studies with DES in rodent models predict marked abnormalities in the adult prostate including increased susceptibility to adult-onset carcinogenesis following early diethylosorbitol exposures (Rajfer and Coffey 1978; Arai et al. 1983; Prins et al. 2001; Huang et al. 2004). Short exposure of bisphenol A (10 μg/kg BW/day) on neonatal rat model showed significantly increased incidence and grade of prostatic intraepithelial neoplasia (Kaufman and Vermeulen 2005). A more extensive epidemiologic study of capacitor manufacturing plant workers highly exposed to PCBs revealed a strong exposure–response relationship for PCa mortality (Prince et al. 2006).

1.7.3 In-vivo and in-vitro models for studying BPH pathogenesis:

Cellular and animal models of BPH have been studied extensively in order to find satisfactory and cost-effective therapeutic options for the patients, in which surgical intervention carries a high risk. The difficulties in obtaining long-term follow-up data as well as follow-up biopsy tissues motivated to develop animal and cell line models. The study of BPH pathogenesis is also hampered because of lack of suitable models and unavailability of commercial cell line.

Men develop spontaneous BPH and it has only been described in the dog and chimpanzees (Steiner et al. 1999). Differences in anatomic structures, limitations of transgenic technology, ethical issues and high cost have made the use of dogs and chimpanzees in BPH research less ideal. Alternatives to the study of spontaneous disease in other species are in-vivo induced BPH models by steroid hormones, xenografts and in-vitro models (Table 1.2) (Mahapokai et al. 2000).

<table>
<thead>
<tr>
<th>MODEL</th>
<th>BENEFIT</th>
<th>DRAWBACK</th>
</tr>
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<tbody>
<tr>
<td>Xenograft</td>
<td>Human cells, BPH types</td>
<td>Immune function, genetics</td>
</tr>
<tr>
<td>Tissue recombination</td>
<td>Human cells, SEI, in-vitro and in-vivo</td>
<td>Immune function</td>
</tr>
<tr>
<td>Human BPH cell line</td>
<td>Human cells, in-vitro</td>
<td>Immune Function</td>
</tr>
<tr>
<td>Chimpanzee</td>
<td>Anatomy, spontaneous, in situ</td>
<td>Genetics, SH, cost, anatomy</td>
</tr>
<tr>
<td>Dog</td>
<td>Literature, spontaneous, in situ</td>
<td>Genetics, SH, cost, anatomy</td>
</tr>
<tr>
<td>Rat</td>
<td>In vivo, cost and time</td>
<td>Genetics, anatomy</td>
</tr>
<tr>
<td>Mouse (Transgenics)</td>
<td>Pathway analysis, in situ</td>
<td>Lacks multifactorial initiation, anatomy</td>
</tr>
</tbody>
</table>

Key: stromal–epithelial interactions (SEI); special housing (SH)

Table 1.2: Different models to study BPH pathogenesis: Benefits and drawbacks
1.7.3.1: Human Cells
Epithelial and stromal cells cultured from normal human prostates and from prostatectomy specimens from patients with BPH as an alternative for researchers to understand BPH pathogenesis. Most of the available human prostate cell lines are derived from malignancies and hence are not suitable for studying BPH.

1.7.3.2: Hormone Induced Model
As the age advances in man, estrogen to androgen ratio alters which leads to the (Belanger et al. 1994) enlargement of the prostate. This concept has led to hormone induction models of BPH. Like men, dogs and rodents have hormone responsive prostates making them particularly important in BPH research. The administration of androgens and estrogens to recreate a hormonal milieu in dog and rodents as similar to men as they age (Walsh and Wilson 1976; DeKlerk et al. 1979; Aumuller et al. 1982; Bartsch et al. 1987; Juniewicz et al. 1989; el Etreby et al. 1991; Takezawa et al. 1992; Winter et al. 1995; Constantinou and Omata 1996; Mahapokai et al. 2000; Zhou et al. 2009). Due to less ethical, similar anatomic and genetic makeup and low costs, rodents become best workable organism for BPH research. Transgenic technology has further opened the rodent model for BPH research. Other models of prostatic hyperplasia include gene over-expression of FGF3 (Muller et al. 1990), FGF7 (Kitsberg and Leder 1996) and p27Kip1-gene knockout mice (Cordon-Cardo et al. 1998). Interestingly, LXR null mice develop prostatic stromal hyperplasia and provide a unique model for this type of prostatic hyperplasia (Kim et al. 2009).

1.7.4 Treatment options for BPH

1) Medical therapy:
   a) Alpha blockers
   b) 5α-reductase inhibitors
   c) Phytotherapy

2) Surgery:
   a) Transurethral resection of the prostate (TURP)
   b) Open prostatectomy
   c) Minimally Invasive Surgical Therapies
   d) Transurethral incision of the prostate (TUIP)
   e) Laser prostatectomy

1.7.4.1a: Alpha blockers:
Prostatic tissue contains high levels of both $\alpha_1$ and $\alpha_2$ adrenoceptors – 98 percent of the $\alpha_1$ adrenoceptors are associated with stromal elements of the prostate (Kobayashi et al. 1993). Thus $\alpha_1$-receptor blockers relax smooth muscle, resulting in relief of bladder outlet obstruction that enhances urine flow (Jepson and Bruskewitz 2000). It was demonstrated in
In 1978, phenoxybenzamine, a nonselective $\alpha_1/\alpha_2$ blocker, was effective in relieving the symptoms of BPH (Caine et al. 1978). Thus, $\alpha_1$ selective antagonists such as terazosin, doxazosin, and prazosin were developed that had fewer side effects than phenoxybenzamine (Lepor 1995). Doxazosin, alfuzosin, and terazosin have gained favor in clinical practice because they are longer acting than prazosin. Due to side effects, many $\alpha_1$ selective antagonists need to be titrated and are often started at the lowest dose and built up over time to the maximal dose or a dose where clinical effects are satisfactory.

1.7.4.1b: 5α-reductase inhibitors
The enzyme 5α-reductase is crucial for the conversion of testosterone to DHT (Bartsch et al. 2002). DHT, once created, enters the nuclei initiating transcription of messenger RNA (mRNA) which then synthesize proteins such as enzymes in the cytoplasm. Inhibitors of 5α-reductase, finasteride, and dutasteride potentially decrease serum and intra-prostatic dihydrotestosterone levels, thus reducing prostatic tissue growth (Boyle et al. 2004).

1.7.4.1c: Phytotherapy:
Phytotherapy, or the use of plant extracts, is becoming widely used in the management of many medical conditions including BPH (Wilt et al. 1998). The action mechanisms of phytotherapeutic agents are poorly understood but have been proposed to be (i) anti-inflammatory, (ii) inhibitors of 5α-reductase, and more recently (iii) through alteration in growth factors (Lowe and Fagelman 1999). The most popular phytotherapeutic agents are extracted from the seeds, barks, and fruits of plants which are as follows:

1. Saw Palmetto Berry (*Serenoa repens*)
2. African plum tree (*Pygeum africanum*)
3. Pumpkin Seed (*Cucurbita pepo*)
4. Rye Pollen (*Secale cereale*)

1.7.4.2: Surgical treatments:
The oldest and most invasive therapy for BPH is open prostatectomy (Serretta et al. 2002b), commonly done through a transvesical approach, but may be done retropubically. Early complications of this operation include hemorrhage, sepsis, and urinary retention with the late complication being bladder neck stricture (2-3%) (Han et al. 2002). Transurethral resection of the prostate (TURP) has lower morbidity but open prostatectomy produces
equivalent, if not superior improvement with a similar or lower re-operation rate (Serretta et al. 2002a).

Approximately 90% of prostatectomies are done by TURP, most common surgical treatment for BPH (Han et al. 2002). TURP involves surgically debulking the periurethral and transitional zones of the prostate to relieve obstruction. Debulking is done by electrocautery in the standard TURP through endoscopic instruments introduced into the urethra and bladder. Tissue is resected in small pieces until the adenoma is removed and a new channel for passage in the prostatic urethra created, much like fashioning a pumpkin for Halloween with the capsule left behind.

Transurethral incision of the prostate (TUIP), a similar approach to a TURP, is used except that no surgical debulking is undertaken. Between one and three incisions are made into the prostate at the level of the bladder neck back almost to the insertion of the ejaculatory ducts. This releases the “ring” of BPH tissue at the bladder neck, creating a larger opening (Aho and Gilling 2003). There is a reduced risk of morbidity such as haemorrhage. In some instances, ejaculation may be preserved in younger men, especially if one incision is made. The procedure only works if the tissue in the periurethral area is not too bulky, otherwise a “ball-valve” mechanism of adenoma may develop.

Laser energy may be used to produce coagulation necrosis, vaporisation of tissue or resection of tissue (Chen et al. 2010). Laser as an energy source has an advantage of standard electrocautery by being relatively bloodless and does not carry the risk of hyponatraemia, which may occur via absorption of irrigant in a standard TURP (Yip et al. 2011). There are several evolving therapies for BPH involving lasers including Holmium laser resection of the prostate (HoLRP), Holmium laser enucleation of the prostate (HoLEP), Holmium laser ablation of the prostate (HoLAP), Neodymium:yttrium-aluminium-garnet (Nd:YAG) and Potassium-titanyl-phosphate (KTP) (Bouchier-Hayes et al. 2006).

1.7.5 Future Treatments
Evidence from the use of botulinum toxin in other lower urinary tract disorders of muscle spasticity (e.g. detrusor hyperreflexia, detrusor sphincter dyssynergia) has led to its expanded application in non-neurogenic conditions such as idiopathic detrusor overactivity, detrusor underactivity (Kuo 2004). Although its mechanism of action in the prostate is unclear, botulinum toxin has been shown to block the release of neurotransmitters such as acetylcholine at the neuromuscular junction as well as in autonomic neurons (Maria et al.,
There may also be significant inhibitory effects on urethral norepinephrine release (Brisinda et al. 2009) and intraprostatic injection of botulinum toxin induces selective denervation and subsequent atrophy of the glands via apoptosis (Kuo and Liu 2009). Thus due to the hyperplasia of connective and smooth muscular tissue in BPH, the prostate would seem to be an ideal location for botulinum toxin to have a pharmacological and clinical effect (Leippold et al. 2003).

Recently, it has been reported that Vitamin D has astonishing potential as a therapeutic agent of BPH (Manchanda et al. 2014). Vitamin D is produced in the skin by the enzymatic modification of cholesterol after exposure to ultraviolet B radiation. 1α,25 dihydroxyvitamin D3 (1α,25(OH)2D3), the active form of vitamin D, is produced in the kidney by hydroxylation of its precursor, 25-hydroxyvitamin D3 (25(OH)D3), and plays a central role in calcium homeostasis and bone remodeling (Roberts et al. 2004). It is also a potent regulator of cell growth and differentiation of prostatic cells, having an antiproliferative action on prostate cells (Peehl et al. 1994). The prostate cells can convert Vitamin-D in its active form, and are also known to express Vitamin D receptor (VDR) thus showing a potential role of Vitamin-D in prostate gland maintenance (Crescioli et al. 2005). Apart from that, many Vitamin-D analogs are known to inhibit cellular pathways, thereby inhibiting proliferation and inflammatory response (Adorini et al. 2010).

1.7.2.B: Prostate Cancer (PCa)

PCa is the most prevalent and is the second most frequently diagnosed cancer and sixth leading cause of cancer-related deaths among men in the world (Jemal et al. 2009). Its etiology, although not clear, is partly attributed to multigenic and epigenetic mechanisms (Maitland and Collins 2005; Shen and Abate-Shen 2010; Maitland et al. 2011; Oldridge et al. 2011). Gleason and others described that when the transition of normal gland into adenocarcinoma of prostate takes place, its normal histological structure is disrupted resulting in abnormal proliferation of the glandular structure, destruction of basement membrane and progressive loss of basal cells (<1%) (Gleason 1966; Maitland et al. 2011). In addition, AR(+) luminal cells increase and contribute in bulk of prostate mass (>99%) in PCa (Grisanzio and Signoretti 2008).

1.8 Link between BPH and PCa:

An association between BPH and PCa was recognized first time by Sommers, 1957 in autopsy studies of prostate gland (Sommers 1957). Since then, several studies confirmed these findings by examining the tissue histology, biochemistry, genetics and lesser extend to
epidemiology of the two diseases (Orsted et al. 2011). Histologically, BPH is defined as microscopic or macroscopic nodules with hyperplasia of stromal cells and epithelial cells and arises in the transitional zone of the prostate. Despite of its prevalence, the exact etiology of BPH is unknown. Similarly, the etiology of PCa is also not fully understood. Although, it is widely accepted that PCa is preceded by prostatic intraepithelial neoplasia (PIN) (Merrimen et al. 2009; Davidsson et al. 2011; Montironi et al. 2011), it is unclear whether PIN stems directly from normal prostatic tissue or originates from hyperplasia (De Marzo et al. 2010). (Fig 1.16) Despite of differences, BPH and PCa share many common features, including hormone-dependent growth and response to anti-androgen therapy (Andriole et al. 2010). Moreover, studies have indicated another common risk factors association with both the diseases such as chronic inflammation, metabolic disruption, and genetic variation (Alcaraz et al. 2009; De Nunzio et al. 2011; De Nunzio et al. 2012). Although, both diseases are affected by several common pathophysiological mechanisms (Fig 1.17). It is not obvious whether, BPH is the first step in the pathway to PCa. Epidemiological study by Simons et al 1993 demonstrated null association between PCa and BPH, and also reported PCa related mortality in men with BPH (Simons et al. 1993). In support of the null associations, Prostate Cancer Prevention Trial (PCPT) reports also suggested that BPH is not associated with PCa incidence (Thompson et al. 1997; Schenk et al. 2011).

Contrary to the findings from these landmark trials, combined analysis of a prospective study of 340 men with BPH and a retrospective study of 290 men with PCa showed a fourfold increased risk of disease coexistence when compared with a similar number of age-matched controls (Armenian et al. 1974). Recently, autopsy studies reported similar results (Orsted et al. 2011; Orsted and Bojesen 2013).

Although the precise mechanism of tumourigenesis in prostate is still in debate, it is widely accepted that cancers can arise from normal cells which may accumulate mutation, genetic changes, and molecular pathway alterations that disrupt self-renewal control capacity. (Table1.3)
Figure 1. 16: Comparative histology of a) Normal, b) Hyperplasic and c) malignant prostate gland

Figure 1. 17: Shared risk factors between benign prostatic hyperplasia (BPH) and prostate cancer (depicted by black arrows). It remains unclear whether BPH is a premalignant lesion and intermediary stages (depicted by the red arrow) exist.
Factors | Normal Prostate | BPH | PCa
---|---|---|---
Prostate specific factors

| 5a-reductase | Normal | Up-regulated | Up-regulated |
| Androgen Receptor (AR) | Normal | Up-regulated | Up-regulated |
| AR co-activator | Normal | Up-regulated | Up-regulated |
| Androgen co-repressor PSA level in serum | Normal (0-4ng/ml) | Up-regulated (2-8ng/ml) | Up-regulated (4-10ng/ml) |

Growth factors

| | FGF-2,7,9 | FGF 1,2,9 | FGF-1,2,6,8 |
| | IGF 1,2 | IGF-2 high | IGF-1 high |
| | IGFBP-2 | IGFBP-3 | IGFBP-2 high IGFBP-3 high |

NE cells | Normal | Number decrease | Number increase |

Luminal cell factors

| | Intracellular space normal | Intracellular space increase | Intracellular space decrease |
| | Vimentin | Vimentin increase | Vimentin over exp |
| | PSMA normal | PSMA decrease | PSMA increase |

Basal cells | Present | Present | Absent |

Stromal cell factor

| | Fibroblast content normal | Fibroblast content increase | Fibroblast content increase |
| | NMMHC | NMMHC increase | NMMHC |
| | Elastin | Elastin decrease | Elastin increase |
| | SMMHC | SMMHC decrease | SMMHC decrease |

Stem cell markers

| | CD44, P63, Sca-1, CD133, CD117, Trop2, CD49f, p27kip1, CK 5(+), 8(-), PSCA | CD44, p63, Sca-1, CD133, p27kip1, CD117, Trop2, CD49f, AR, CK5(+), 8(-), PSCA high | CD44, Sca-1, CD133, CD117, Trop2, CD49f, CK5(-), PSCA high, AR |

Table 1. 3: Molecular alterations in BPH and PCa, NMMHC: non-muscle myosin heavy chain, SMMHC: Smooth Muscle myosin heavy chain, FGF: Fibroblast Growth factor, IGF: Insulin-like growth Factor, IGFBP: IGF Binding Protein, PSMA: Prostate-specific membrane antigen

1.9 References


To Understand The Etiopathogenesis of Benign Prostate Hyperplasia at Biochemical, Cellular and Molecular level.


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CHAPTER-1

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Yip SK, Chan NH, Chiu P, Lee KW, Ng CF. 2011. A randomized controlled trial comparing the efficacy of hybrid bipolar transurethral vaporization and resection of the prostate with bipolar

