The Prostate Gland

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Learning Objectives

- Development and gross anatomical features
- Lobes and zones
- Microstructure and functional regulation
- Components of prostatic fluid
- Disorders of prostate gland

2.1 Introduction

The name 'prostate' is originally derived from a Greek word 'prohistani' (means 'to stand in front of'). The prostate is the largest accessory sex gland of males. It is a musculo-glandular, exocrine gland that secretes alkaline fluid which constitutes about 20–30 % volume of the seminal fluid. Changes in the prostatic fluid composition and/or secretion affect sperm functions and may lead to male infertility. The gland is often associated with disorders of elderly, benign prostatic hyperplasia (BPH) and carcinoma.

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2.2 Development

The ventral division of cloaca which is the terminal part of hindgut, forms the urogenital sinus. During ninth–tenth week of development, the mesenchyme surrounding the urogenital sinus interact with endoderm of proximal part of urogenital sinus which later forms the proximal part of urethra. As a result of these interactions, the initial outgrowths arise from the lateral aspect of the endodermal tube. The outgrowths form the outer glandular zone of prostate. The subsequent outgrowths arise from its dorsal wall which forms the internal glandular zone. The outgrowths develop into five distinct groups of epithelial buds by the end of the 11th week and are completed by the 16th week. According to the classification given by Lowsley, five groups of epithelial buds give rise to five lobes, namely, the median, right and left lateral and posterior and anterior lobes (Lowsley 1912). These lobes of prostate gland are recognized till the 20th week of gestation. With an advance in gestational age, only three lobes are recognizable–two lateral lobes and a median lobe (Standring 2005). The epithelial buds branch and rebranch ending into complex ductal system that meets the differentiating mesenchymal cells (see Fig. 2.1a–e). The mesenchymal cells develop around the tubules by the 16th week and become denser at the periphery to form the prostatic capsule (Grayhack and Kozlowski 1996).

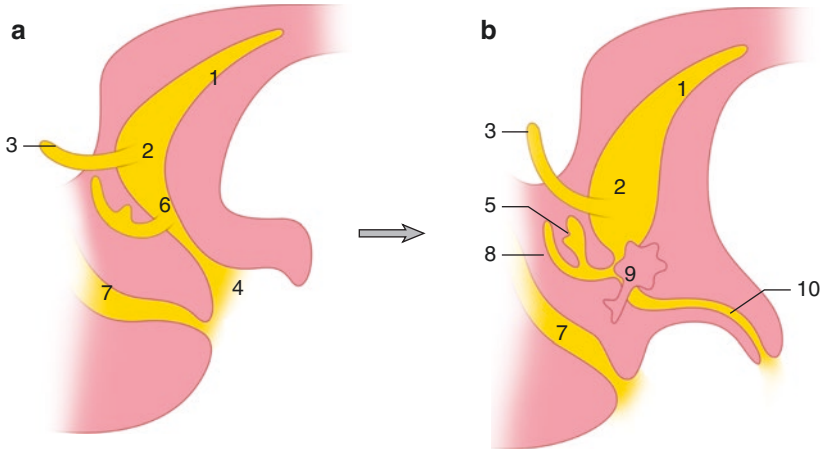

Fig. 2.1 Development of prostate gland (**a**–**e**): the endodermal outgrowths from the prostatic urethra into the surrounding mesenchyme form the gland primordium which further proliferate and enlarges. *1* allantois, *2* urinary bladder, *3* ureter, *4* definitive urogenital sinus, *5* seminal vesicle, *6* pelvic part of urogenital sinus, *7* anorectal canal, *8* ductus deferens, *9* prostate, *10* penile urethra, *11* endodermal tube, *12* glandular outgrowths, (**f**) prostatic glands, (**g**) enlarged view of tubuloalveolar gland

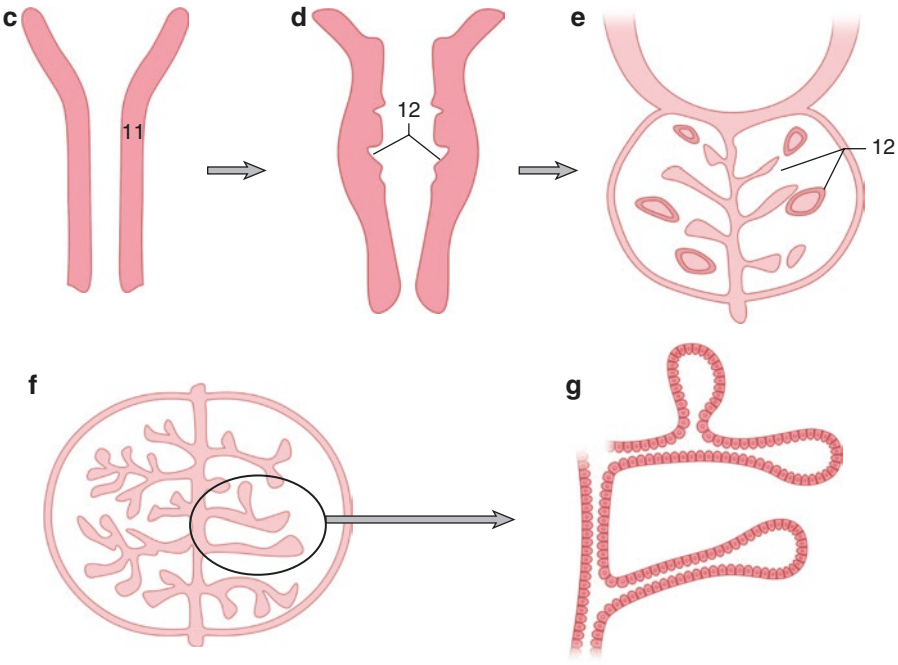

Fig. 2.1 (continued)

2.3 Gross Anatomical Features

The normal adult gland is about the size of a walnut and resembles a cone measuring approximately 4 cm (transverse) × 3 cm (vertical) and 2 cm (anteroposterior) and weighs approximately 20 grams in adults. The gland comprises of glandular and stromal elements, tightly fused within a capsule (Grayhack and Kozlowski 1996; Lee et al. 2011).

The prostate is positioned subperitoneally below the pelvic diaphragm. It lies posterior to the symphysis pubis, anterior to the rectum and inferior to the urinary bladder surrounding its neck (Lee et al. 2011). Being pyramidal in shape, it has a base superiorly, a neck inferiorly along with anterior, posterior and two inferolateral surfaces. The anterior surface lies behind the pubic arch (see Fig. 2.2). The urethra pierces the prostate near the middle of the base and exits on the anterior surface above and in front of its apical portion. The inferolateral surfaces are related to the lateral pelvic wall. The posterior surface of prostate and seminal vesicles is separated from the rectum by a thin layer of connective tissue called 'Denonvilliers' fascia' (Hammerich et al. 2009). This fascia forms a surgical plane of excision for rectal cancers. The rectum along with the fascia is separated anteriorly from seminal vesicles in males and vagina in females (Decker and du Plessis 1986).

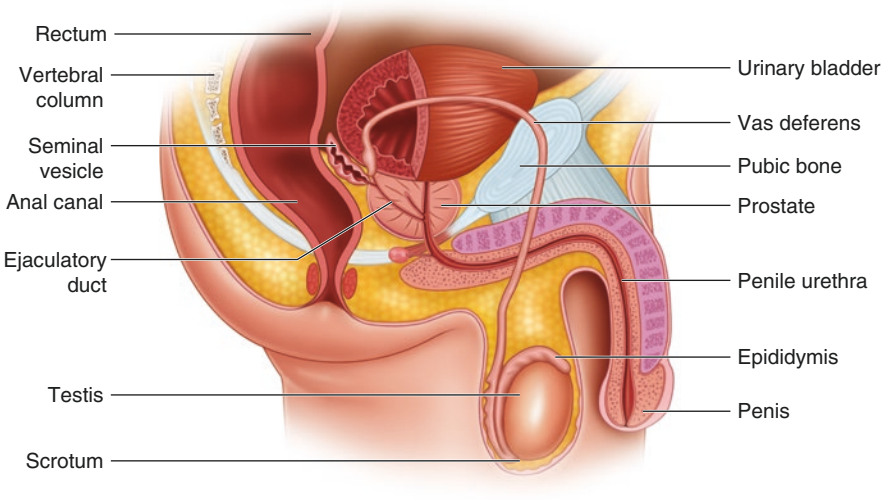

Fig. 2.2 Sagittal section of the male pelvis showing relations of the prostate

The ejaculatory duct traverses the base on its posterior surface and terminates adjacent to the seminal colliculus, also known as verumontanum (Grayhack and Kozlowski 1996).

2.4 Anatomical Lobes and Zones

The anterior lobe lies in front of prostatic urethra and continuous with lateral lobes on either side. The median lobe is situated behind the urethra and in front of ejaculatory ducts. The posterior lobe lies behind the median lobe and below ejaculatory ducts. Another simplified and clinically important way of describing prostatic morphology has been proposed. There are four prostatic zones, namely, the central zone (CZ), the transitional zone (TZ), the peripheral zone (PZ), and the periurethral gland or anterior fibromuscular stroma (AFMS) (McNeal 1981).

The cone-shaped CZ occupies approximately 25 % of the glandular prostate. CZ surrounds ejaculatory ducts and extends from the neck of the bladder to verumontanum. This zone incorporates median and posterior lobes. A major proteolytic enzyme of the seminal fluid, pepsinogen II, is produced by the cells of the central zone.

TZ represents only 5 % of the gland. TZ surrounds the distal part of preprostatic urethra near the apex of central zone and ejaculatory ducts. It incorporates part of anterior and median lobes. It is the exclusive site of BPH and, less commonly, adenocarcinoma.

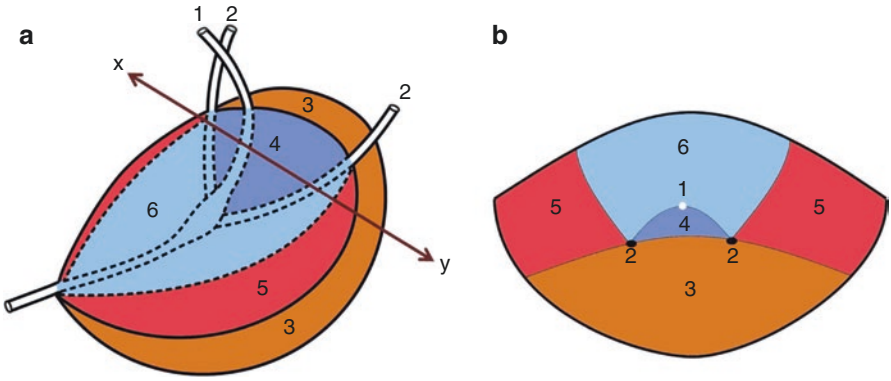

Fig. 2.3 Schematic diagram showing lobes of prostate gland in superolateral view (**a**) and transverse section (**b**) across plane *x–y*. *1* urethra, *2* ejaculatory ducts, *3* posterior lobe, *4* median lobe, *5* lateral lobes, *6* anterior lobe

PZ constitutes 70 % of the glandular prostate. This zone encloses the central and transition zones and preprostatic urethra except anteriorly. It extends distally to enclose lower part of prostatic urethra below verumontanum. The PZ contains the lateral lobes and the remaining part of the posterior lobe (De Krester et al. 1982). In this zone, carcinoma, chronic prostatitis and postinflammatory atrophy are relatively more common. With age, CZ undergoes atrophic changes and TZ enlarges due to BPH which compresses PZ (Standring 2005).

AFMS comprises less than 1 % of the glandular prostate; it fills the space between PZs anterior to preprostatic urethra and incorporates the major part of the anterior lobe. It is predominantly fibromuscular with little or no glandular structures (Grayhack and Kozlowski 1996; Lee et al. 2011; see Figs. 2.3 and 2.4).

2.5 Microstructure

The human prostate is composed of 30–50 tubuloalveolar glands and fibromuscular stroma. It is enclosed by a strong fibrous capsule which sends fibromuscular septa within the gland thereby dividing the gland into smaller regions or lobules. The glands are elongated with sac-like ends and have irregular size (see Fig 2.1g). The glands are arranged in inner mucosal layer, middle submucosal layer and outermost layer which have the main prostatic glands. The glands in the mucosal layer open directly into the urethra, whereas glands of outer two layers open into the prostatic sinuses on the posterior wall of urethra on either side of urethral crest. Each prostatic gland opens into the urethra through a prostatic duct. The characteristic feature seen in the lumen of these glands is concretions formed by aggregations of dead epithelial cells and secretory precipitations. The fibromuscular stroma consists of smooth muscle cells, contractions of which help in forcing the secretions into the urethra during ejaculation (Standring 2005; Ross and Pawlina 2006). There are different types of

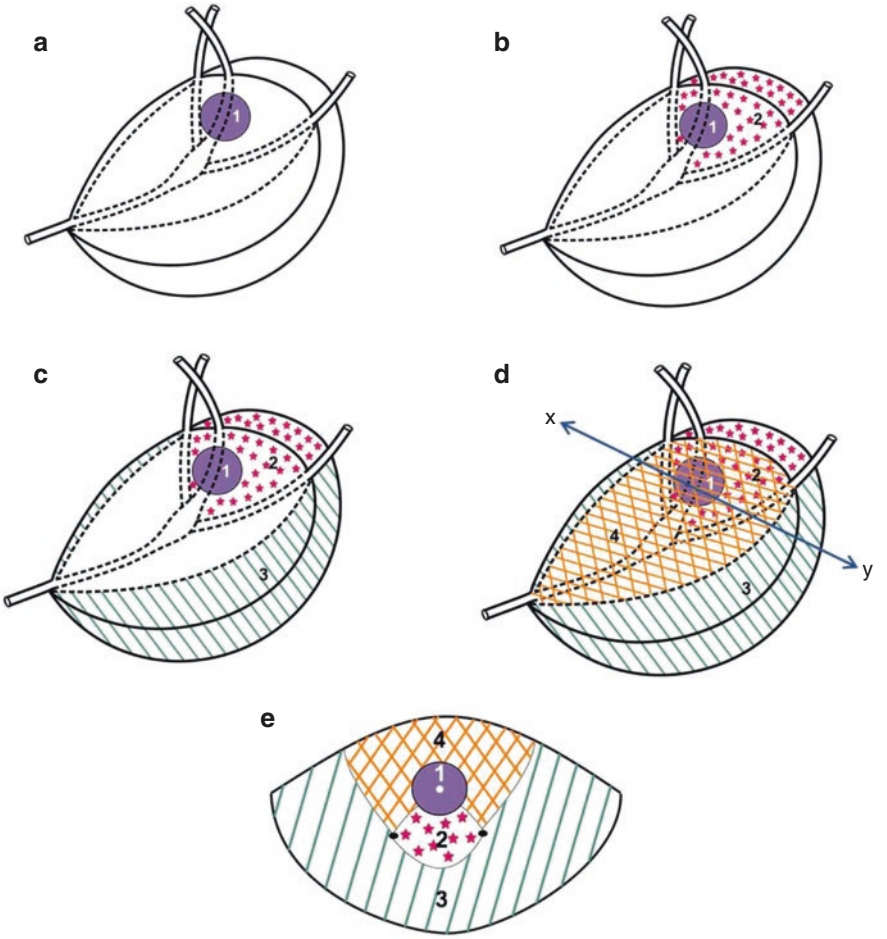

Fig. 2.4 Schematic diagram showing zones of prostate gland in superolateral view (**a**–**d**) and transverse section (**e**) across plane *x*–*y*. *1* transition zone (part of anterior and median lobes), *2* central zone (part of median and posterior lobes), *3* peripheral zone (lateral and remaining posterior lobes), *4* anterior fibromuscular stroma (anterior lobe)

cells in the glandular epithelium: secretory tall columnar or luminal cells, basal cells, stem cells, amplifying cells and neuroendocrine cells (see Figs 2.5 and 2.6).

2.5.1 Luminal Cell or Secretory Cell

The secretory cell (SC) is the predominant cell type and opposes the lumen. SC is 20 μm in height and has a round nucleus located at the base. The basal cytoplasm contains free ribosomes, rough endoplasmic reticulum and mitochondria, while the apical cytoplasm has lysosomes and dense bodies. The dense bodies contain a yellow pigment, lipofuschin. In elderly men, these pigments are found in the base or

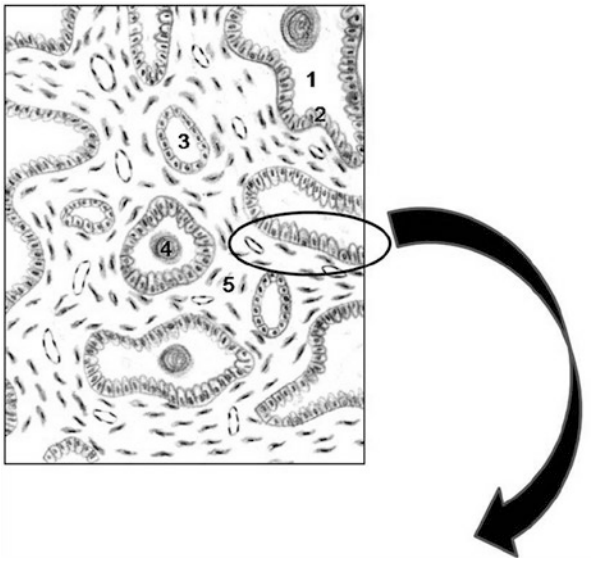

Fig. 2.5 Schematic diagram showing microstructure of prostate gland. *1* glandular acinus, *2* glandular epithelium, *3* duct of prostatic gland, *4* prostatic concretions, *5* fibromuscular stroma

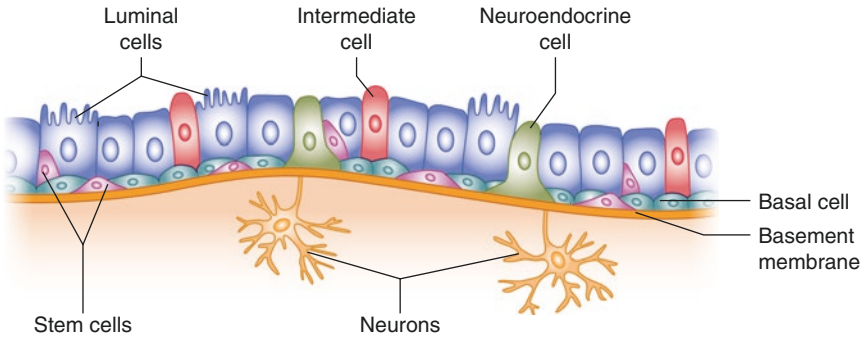

Fig. 2.6 Schematic diagram showing cells of prostatic epithelium

supranuclear areas of glands. Villiform projections are present in the apical cytoplasm, and they extend into the lumen (see Fig. 2.6). However, these projections are not found in areas associated with secretory granules or cells that have released their contents (Grayhack and Kozlowski 1996). SCs have comparatively limited proliferating capacity, as suggested by their high mitotic index, i.e. the ratio of the mitotic phase-arrested cell to the total number of cells (Ikeda et al. 2000). These cells express nuclear androgen receptor, cytokeratins 8 and 18 as well as the cell-surface marker CD57 (Schalken 2005). They are androgen-dependent cells and secrete fluid, prostate-specific antigen (PSA) and prostate acid phosphatase (PAP) into the glandular lumen. The activity of acid phosphatase is mainly localized within

the secretory vacuoles and lysosomes, while that of amino peptidase and PSA are in the apical cell border and cytoplasm, respectively (Grayhack and Kozlowski 1996).

Androgen deprivation decreases the number of SCs. Following damage and infection, with testosterone replacement, the luminal compartment rapidly regenerates itself from the basal compartment (Lee et al. 2012).

2.5.2 Basal Cell

Basal cells (BCs) are found between the luminal cells and the underlying basement membrane (see Fig. 2.6). They are polygonal in shape and have large irregular-shaped nuclei. BCs lack secretory vesicles. They possess mitochondria, endoplasmic reticulum, free ribosomes, Golgi apparatus and pinocytic vesicles. Their specific markers are cytosolic cytokeratins 5 and 14 and CD44 on the cell surface (Grayhack and Kozlowski 1996; Long et al. 2005). The androgen receptors are expressed at very low level in the basal layer.

2.5.3 Stem Cell

A stem-like cell population in the basal layer is responsible for the development of epithelial cells in the prostate (see Fig. 2.6; Long et al. 2005; Peehl 2005). The stem cells self-renew by a symmetrical division, i.e. the daughter cells demonstrate similar growth and duplication potential as the mother cell. Following asymmetric division of the stem cell, the two daughter cells differ in characteristics, i.e. one daughter cell retains stem cell properties and the other becomes differentiated daughter cell. The markers which identify stem cells are CD133, CD44, $\alpha_2\beta_1$ integrin, breast cancer-reserved protein (BCRP-1), ATP-binding cassette subfamily G member 2 (ABCG-2), telomerase reverse transcriptase (TERT) and CK5/CK14 (Mimeault et al. 2008).

2.5.3.1 Differentiation of Stem Cells

Linear differentiation model

According to this model, stem cell found in the basal layer undergoes asymmetric division to give rise to stem cell that has unlimited self-renewal capacity and progenitor cells which further divide and differentiate to intermediate cells. The intermediate cell subsequently differentiates into either luminal or neuroendocrine cells (Taylor et al. 2010). This model is derived on the basis of studies on mouse prostatic tissue.

Bidirectional differentiation model

Bidirectional differentiation model is developed based on the study of prostatic cells and tissue of mouse as well as human. The model is supported by the existence of intermediate cells that express both BC- and SC-specific markers, e.g. cytokeratins 8 and/or 18 and cytokeratins 5 and/or 14 in both developing and adult stages of prostate development. In this model, one population of stem cell maintains its own

cell number through self-renewal, and another is committed to further division and differentiation, giving rise to intermediate cells. This intermediate cell differentiates to a variety of lineage-specific progenitors which further differentiate to basal, luminal and neuroendocrine cells (Wang et al. 2001).

Independent lineage model
The third independent lineage model suggests that stem cells are also present among the luminal cells. This is based on the presence of a typical cell castrate-resistant Nkx3.1-expressing cells (CARNs). CARNs cells have the capacity to self-replenish in vivo or undergo division to give rise to a variety of progenitors of specific cell lineage, i.e. basal, luminal and neuroendocrine cells. The basal stem cells self-replenish or differentiate into basal cell through lineage-specific progenitors. The basal and/or luminal stem cells can be multipotent and generate the opposing lineage with basal stem cells giving rise to SCs and luminal stem cells giving rise to BCs (Taylor et al. 2010).

2.5.4 Intermediate or Amplifying Cells

Intermediate cells are proliferating cells which express markers present in both the BCs and SCs. These cells express luminal marker cytokeratins 8 and 18 in the basal layer, whereas some cells in the luminal layer express basal cell cytokeratins 5 and 14 (see Fig. 2.6; Long et al. 2005).

2.5.5 Neuroendocrine Cells

Neuroendocrine cells (NECs) are highly specialized epithelial cells and are androgen-independent cells which are distributed all over the basal layer. They are of two types: (a) the 'open' cell type that has long extensions that connects to the lumen and (b) the 'closed' type that do not have direct contact with the lumen. NECs possess uneven dendritic processes that extend between adjacent cells (see Fig. 2.6). The major markers are chromogranin A, serotonin, bombesin, neuron-specific enolase and calcitonin (Vashchenko and Abrahamsson 2005). Although its function is still not clearly understood, these cells regulate growth, differentiation and homeostatic regulation of the secretory processes (Abrahamsson and diSant'Agnese 1993).

2.6 Regulation of Prostatic Function

2.6.1 Androgens

Testosterone synthesized by the testis and adrenals, diffuses into the prostatic epithelium and is rapidly converted to dihydrotestosterone (DHT) by the enzyme 5α-reductase. DHT has fivefold higher affinity for the androgen receptor than

testosterone. In the resting state, unligated androgen receptors in the cytoplasm are bound to heat shock proteins (HSPs), viz. HSP90, 70, 56 and 23, which stabilize the tertiary structure of androgen receptor in a confirmation that facilitates androgen binding. Upon binding of androgens to the androgen receptor, the HSPs dissociate leading to androgen receptor dimerization and subsequent translocation into the nucleus, where the dimerized androgen receptor binds to the androgen response elements (AREs) in the promoter/enhancer regions of target genes. The activated DNA-bound androgen receptor dimer complex then recruits co-regulatory proteins (co-activators or co-repressors) and the general transcription machinery. The co-activators, members of the p160 family that have histone acetyltransferase activity, such as NCOA1-3, TIP60, etc., alter the chromatin structure to a form which is more accessible for the transcription machinery. In contrast, the co-repressors, e.g. silencing mediator of retinoid and thyroid (SMRT) hormone receptors and nuclear receptor co-repressor (NCOR), mediate chromatin condensation leading to transcription silencing. Androgen receptor-regulated target genes include PSA, PAP, cyclin-dependent kinase 8 (CDK8) and the p85 catalytic subunit of phosphatidylinositol 3-kinase (PIK3R1) and RAB4A–a member of the Ras oncogene family of proteins. While PSA and PAP are major secretory proteins of the prostate, CDK8 is involved in cell cycle regulation; PI3KR1 activates signalling pathways important for cell proliferation and survival, and RAB4A is involved in receptor trafficking and vesicle fusion. Collectively, the activation of these genes by androgens leads to cell growth, survival and increased production of the secretory proteins (Feldman and Feldman 2001; Taplin 2007).

2.6.2 Estrogens

Estrogen action is mediated in two different ways: endocrine effects acting via pituitary to indirectly lower androgens and local paracrine effects directly targeting the prostate tissue itself. The paracrine effect is mediated by the two types of estrogen receptors- alpha (ERα) and beta (ERβ), which are localized mainly in stromal cells and epithelium, respectively. ERβ complexes with endothelial nitric oxide synthase (eNOS) and hypoxia inducible factor (HIF) which leads to chromatin remodelling and induction of transcription. This activation of ERβ has anti-proliferative effects that balance the proliferative action of androgen on the prostatic epithelia. In contrast, the activation of ERα leads to aberrant proliferation, inflammation and the development of premalignant lesions, though its molecular mechanism has not been worked out. Therefore, estrogens also play a role in the aetiology of prostatic diseases (Harkonen and Makela 2004; Prins and Korach 2008; Ellem and Risbridger 2009).

2.6.3 Prolactin

Prolactin (PRL), a hypophyseal peptide hormone, belongs to the growth hormone family. It has been reported to be locally produced in the prostate. Prolactin

receptors (PRLR) are also found in the prostate. As mentioned earlier, in the developing prostate, prolactin promotes ductal morphogenesis. PRL has a physiological role in stimulating citrate production by regulating the metabolic genes, namely, mitochondrial aspartate aminotransferase, pyruvate dehydrogenase and mitochondrial aconitase via protein kinase C (PKC) signalling pathway (Costello and Franklin 2002). PRL acts as a strong mitogen and survival factor for prostate epithelium, an effect mediated by autocrine signalling through PRLR-Jak2-Stat5a/b pathway. Hence, it has a role during prostate cancer progression, and the inhibition of this pathway leads to apoptosis (Goffin et al. 2011).

2.6.4 Oxytocin

Oxytocin (OXT) is a neurohypophysial nonapeptide hormone with sequence similar to vasopressin, also known as antidiuretic hormone. In normal prostate, oxytocin is found at a concentration ranging from 0.5 to 30 nM. Both oxytocin and its receptor are expressed by the epithelial as well as stromal cells of benign and normal prostate. Its secretion is under regulation of androgens and estrogen, with increased estrogen/androgen ratio stimulating the greatest secretion. OXT inhibits proliferation of stromal and epithelial cells both directly and by regulating the local concentration of androgens. Oxytocin increases the expression and activity of the 5α-reductase enzyme, thus affecting the androgen metabolism. It also increases prostatic muscular tone and contractile activity (Thackare et al. 2006; Nicholson and Whittington 2007; Assinder 2008).

2.6.5 Thyroid Hormones

The existence of prostate-thyroid axis has been reported in the rodents (Mani Maran et al. 1998). Recently, a prospective study showed that men with hypothyroid state had a lower risk of developing prostate cancer (Mondul et al. 2012). The thyroid hormone, 3,5,3′-L-triiodothyronine (T_3), stimulates PSA expression at both mRNA and protein level in the presence of androgens. A functional thyroid hormone response element (TRE) is located in the 5′-promoter region (−198 to −183 upstream from the start codon) of the PSA gene. However, T3 has only a minimal effect on PSA expression in the absence of androgens, and it is yet to be explored how androgen-androgen receptor-ARE complex interacts with T3-TR-TRE complex in modulating PSA expression (Zhu and Young 2001).

2.6.6 Growth Factors

Besides hormones, normal prostate development and homeostasis between epithelial and stromal cells are also regulated by various growth factors. A complex interaction exists between the growth factors themselves, and, in turn, they also are

regulated either by androgen or by other factors. Hence, prostate is very sensitive to any alteration, either up- or downregulation, in the expression of growth factors and/or their receptors.

Insulin-like growth factor (IGF) family includes polypeptide growth factors that have amino acid sequence and functional homology to insulin. IGFs are produced by the stromal cells and act on epithelial cells in a paracrine manner in response to androgen stimulation resulting in enhanced proliferation of the prostatic cells (Reynolds and Kyprianou 2006).

Epidermal growth factor (EGF) and transforming growth factor alpha (TGF α) are structurally and functionally related polypeptides that signal through the same cell surface receptor, viz. EGF receptor (EGFR), a transmembrane tyrosine kinase. EGF is an important activator of normal prostate growth, and its expression is positively regulated by androgens. It is even found in large quantities in the prostatic fluid. However, TGF-α is expressed chiefly in the stroma, while its receptor is expressed by the epithelial cells suggesting that it works in a paracrine /juxtacrine manner in the normal prostate. The upregulation of both EGF and TGF-α is associated with the development of prostate cancer as they exert a mitogenic effect on epithelial cells (Russell et al. 1998).

TGF-β family includes TGF-β1, TGF-β2 and TGF-β3. They are expressed during prostate development and in the adult prostate, both normal and malignant. TGF-β is produced by both stromal and epithelial cells, but its receptors are found only on the stromal cells. It regulates prostatic growth by inhibiting cell proliferation and inducing apoptosis (Russel et al. 1998).

The fibroblast growth factor (FGF) family includes nine structurally related heparin-binding peptides, of which three are implicated in prostate cancer, viz. bFGF, aFGF and KGF. bFGF is produced by both stromal and epithelial cells of the prostate, but its receptor is present only on stromal cells in normal prostate (Sherwood et al. 1992). In contrast, KGF is secreted by the stromal cells while its receptor is present on the epithelial cells. It upregulates epithelial cell proliferation in a paracrine manner (McGarvey and Sterans 1995). Role of aFGF in the development of rat prostate has been shown, but it is not detected in human prostate (Russel et al. 1998).

In a nutshell, the growth factors IGF, EGF, TGF-β and FGF are predominantly stimulators of proliferation, while TGF-β predominantly inhibits prostatic growth.

2.6.7 Bone Morphogenetic Proteins

Bone morphogenetic proteins (BMPs) belong to the TGF-β superfamily and regulate growth, differentiation and apoptosis in many tissues in addition to the bone. The expression of BMPs (viz. BMP-2, -3, -4 and -6) by the normal human prostate and human prostate cancer cell lines has been reported. The higher expression of BMP-6 in malignant prostate tissue indicates that it contributes to prostate carcinogenesis (Shimasaki et al. 2004). In contrast, the expression of BMP-7 is strongly downregulated in prostate cancer tissue compared to normal prostate luminal

epithelium (Buijs et al. 2007). BMP-4 and BMP-7 inhibit branching morphogenesis during prostate gland development (Prins and Putz 2008).

2.7 Components of Prostatic Fluid

2.7.1 Prostate-Specific Antigen

Prostate-specific antigen (PSA) is an androgen-regulated serine protease. It is a member of human tissue kallikrein gene family, located on chromosome 19q13.4. PSA is produced by the secretory epithelial cells in the ducts and acini of the prostate and is present at a concentration of 0.5–2.0 mg/ml in the seminal fluid. Its physiological function is to liquefy the seminal coagulum formed just after ejaculation by cleaving the semenogelins.

The transcription of the PSA gene is positively regulated by androgen receptor that attaches to specific DNA sequences called ARE. There are three regions upstream of the PSA gene which contain the consensus ARE: region −156 to −170 in the PSA gene proximal promoter, an androgen responsive region from −365 to –400 and a PSA distal enhancer about 4.2 kb upstream of the transcription start site. Following transcription and translation, PSA is secreted as an inactive proenzyme (proPSA) having 244 amino acids. In the lumen, proPSA is converted to a 237-amino acid long, active PSA by prostatic protease, viz. human kallikrein-2. About 30 % of the PSA in the seminal fluid is in the active form, whereas 5 % remains bound with protein C inhibitor. The remaining PSA undergoes internal cleavage to form catalytically inactive PSA. Both the active and cleaved PSA can enter into the circulation. In the peripheral blood, 70 % to 90 % PSA remains bound to protease inhibitors, chiefly alpha 1 anti-chymotrypsin while 10 % to 30 % is the inactive, cleaved PSA which circulates as free PSA (Diamandis 2000; Balk et al. 2003). This ratio of free to total PSA (fPSA /tPSA, termed the PSA index) is lower in many patients with prostate cancer and can discriminate between normal and malignant prostate.

2.7.2 Prostatic Acid Phosphatase

Prostatic acid phosphatase (PAP) is a dimeric glycoprotein enzyme. PAP is synthesized by the columnar secretory epithelia of the prostate. The enzyme is expressed at puberty and is androgen regulated. Two forms of PAP are known–cellular (cPAP) and secreted (sPAP); both are transcribed from the same gene but undergo different post-translational modifications. Interestingly, though PAP shows only 50 % sequence similarity with the lysosomal acid phosphatase, the amino acids in the active site of both enzymes are conserved. PAP catalyses the hydrolysis of various phosphate esters, viz. phosphorylcholine and phosphocreatine which are energy-rich compounds present in the seminal fluid. The presence of high amount of PAP in seminal fluid (~ 1 mg/ml) suggests a role in fertility, perhaps in increasing sperm

mobility, but this role of sPAP is controversial (Kong and Byun 2013). Many studies show that higher levels of sPAP are found in seminal plasma of azoospermic men and also an inverse correlation between seminal PAP levels, and sperm concentration has been observed in oligospermic men (Kong and Byun 2013). Normal levels of serum sPAP vary from 1 to 3 ng/ml, while prostate cancer patients show elevated levels which increase as the disease progresses. In contrast, levels of cPAP are inversely related with progression of prostate cancer (Hassan et al. 2010; Muniyan et al. 2013).

2.7.3 Citric Acid

Citrate level in the normal prostatic fluid is about 400–1500 times the level found in blood plasma. Though its precise function in semen is not known, it is possibly required to maintain osmotic/electrolytic equilibrium in the semen. In normal mammalian cells, citrate is crucial in the citric acid cycle or Kreb's cycle for ATP generation. However, in the peripheral zone of the prostate, increased accumulation of zinc inhibits mitochondrial aconitase activity which oxidizes citrate to isocitrate. Thus, Kreb's cycle in these cells gets truncated, and citrate is secreted in the prostatic fluid. Therefore, the prostatic epithelial cells are also known as 'citrate-producing cells'. In prostate cancer, a decrease in the accumulation of zinc occurs. This 70–90 % reduced tissue levels of zinc do not inhibit aconitase activity; consequently, citrate is oxidized via the Kreb's cycle. Therefore, the malignant cells are referred to as 'citrate-oxidizing cells', and the concentration of citrate in the prostatic fluid is markedly decreased from 100 mM in normal to 8 mM in prostate cancer (Costello and Franklin 2009).

2.7.4 Zinc

High levels of zinc in the prostatic epithelial cells help to carry out the major physiological functions of citrate production and secretion. High concentration of zinc in the seminal plasma confers its bactericidal activity. Decrease in the levels of zinc and citrate in the normal prostatic cells is an important factor in the development of malignancy. Decreased accumulation of zinc in the prostatic epithelial cells (1000 ug/ml in normal vs. 150 ug/ml in cancerous) may be due to the downregulation of specific zinc uptake transporters proteins, viz. hZIP1. hZIP1 belongs to the ZIP (Zrt/Irt-like Proteins) family of transporters. The hormones, prolactin and testosterone, promote accumulation of zinc in prostate epithelial cells. However, the exact mechanism of zinc accumulation and its regulation in prostatic cells remain to be explored (Franklin et al. 2005). Zinc ions in the prostatic fluid are important for semen coagulation as they trigger a conformational change in the semenogelin proteins which form an insoluble protein complex of the coagulum. The normal concentration of zinc in seminal fluid is about 2.4 mM which is 100-fold higher than that in blood plasma.

2.7.5 Spermine

Spermine is a basic aliphatic polyamine secreted by the prostate gland. Other cellular polyamines are known to stimulate protein and RNA synthesis by binding non-covalently to nucleic acids and structures containing nucleic acid, e.g. ribosomes. Spermine also has strong affinity for phosphate ions, nucleic acids or phospholipids. When semen is kept undisturbed at room temperature, a transparent yellow crystal of spermine phosphate is formed. This is due to the hydrolysis of seminal phosphorylcholine, produced mainly in the epididymis, by acid phosphatase resulting in the release of inorganic phosphate ions. Finally, the phosphate ions react with spermine to form spermine phosphate. The enzyme diamine oxidase, present in the seminal plasma, oxidizes spermine to an aldehyde product that is responsible for the unique odour of semen (Folk et al. 1980).

2.7.6 Prostatic Inhibin

Prostatic inhibin is also known as β-inhibin, β-micro seminoprotein, immunoglobulin binding factor, prostatic inhibin peptide and prostatic secretory protein. It is made up of 94 amino acids and is synthesized and secreted by prostatic epithelium. It is a follicle stimulating hormone (FSH)-suppressing, non-glycosylated, cysteine-rich polypeptide (10.7 kDa). It is not related to dimeric pituitary inhibin but is a single-chain polypeptide of 94 amino acids which constitutes about 20 % of total seminal plasma proteins. Unlike PSA and PAP, prostatic inhibin expression is not dependent on androgens. Its concentration is 100 times more in the prostate than in testis. In contrast to PSA, lower levels of prostatic inhibin are found in the prostate, serum as well as urine of patients with prostate cancer. It has been implicated as a tumor growth suppressor, and silencing of its gene expression has been associated with promoter methylation of EZH2, a polycomb group member protein (Garde et al. 1992; Haiman et al. 2013).

2.8 Disorders of Prostate Gland

2.8.1 Benign Prostatic Hyperplasia (BPH)

BPH is a non-cancerous enlargement of the prostate. It is a very common urological problem among ageing men and leads to lower urinary tract symptoms. Although increase in both stromal and epithelial elements of the prostate occurs in BPH, the major increase in prostate volume is due to increased number of stromal smooth muscle cells. The exact pathogenesis of BPH is unknown, but a role of DHT in causing pathological prostate growth has been demonstrated. Since the enzyme 5-alpha reductase is responsible for conversion of testosterone to DHT in the prostate, inhibitors of this enzyme are used as drugs for reducing the prostate volume. Two subtypes of the enzyme are known with type-2 being the predominant type in the

prostate. However, it has been seen that non-selective inhibitors of 5-alpha reductase (dutasteride) have higher efficacy than selective inhibitor of type-2 isozyme (finasteride) in suppressing the enzyme activity. Alpha-1 receptor blockers target the alpha-1A receptors present on the stromal smooth muscle cells thereby relaxing these muscles and, hence, reducing the dynamic component of bladder outflow obstruction. Both 5-alpha reductase inhibitor and alpha-1 blockers are used either alone or in combination for therapy depending on the disease status (Prabhav and Bairy 2009; Briganti et al. 2009).

2.8.2 Prostate Cancer

Prostate cancer is currently the most common cause of cancer death in men. The exact cause of developing prostate cancer are not known though ageing, ethnicity and heredity are important factors involved in the initiation and development of this cancer. Ageing is considered the most prominent risk factor, with majority of cases being diagnosed in men between 60 and 70 years of age. The role of various genes such as NKX3.1, Myc, ERG, PTEN and EZH2 has been implicated in prostate cancer (Shen and Abate-Shen 2010).

In recent years, the role of xenobiotics such as cadmium, lead, organochlorine pesticides and polychlorinated biphenyls have been implicated with prostate cancer risk in agricultural and general population. (Dich and Wiklund 1998; Settimi et al. 2003; Mink et al. 2008). The carcinogenic effect of the pesticide methyl bromide is due to its methyl group which binds to DNA to form DNA adducts, O6- and N7-methylguanine, which ultimately result in a G:C to A:T transition mutation. These gene mutations represent the early steps in prostate carcinogenesis (Cockburn et al. 2011). Another toxicant, lead, is a potential risk factor for prostate cancer. Its action is possibly mediated by increasing reactive oxygen species generation and/or by reducing the accumulation of zinc, which acts as an inhibitor of cellular growth (Siddiqui et al. 2002). Animal studies have shown that phthalates also may cause proliferative and inflammatory disorders of the rat prostate (Scarano et al. 2009). The other details of prostate cancer are given in the chapter, Male Reproductive Cancers.

2.8.3 5α-Reductase 2 Deficiency or Pseudovaginal Perineoscrotal Hypospadias

5α-reductase 2 deficiency is a result of decreased DHT production due to mutations in the 5α-reductase 2 gene (SRD5A2 gene) which is located on chromosome 2 (2p23). It is an autosomal recessive disorder of male sexual development with more than 50 mutations reported in the gene. The affected males have normal internal reproductive structures; however, they possess external genitalia similar to females, i.e. ambiguous genitalia. The prostate is underdeveloped with fibrous connective

tissue, smooth muscle and no identifiable epithelial tissue, which suggests atrophic epithelium or lack of epithelial differentiation. However, these individuals undergo partial virilization of the external genitalia at puberty (Azzouni et al. 2012).

Key Questions

- Name the different zones of the prostate gland with their clinical relevance.
- Write briefly about the different cell specific markers of the prostatic epithelial cells.
- Name the key components of prostatic fluid.
- Explain briefly the physiological importance of the prostatic fluid components in semen.
- Discuss the regulation of prostate function by androgens.
- Write a short note on the physiological role of growth factors produced by the prostate gland.

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