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# Estrogens and aspects of prostate disease

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**Abstract:** Estrogens have long been associated with the processes involved in prostate carcinogenesis, particularly in cancer suppression. However, the synergistic influence of low concentrations of estrogens, together with androgens, in promoting aberrant growth of the gland has also been recognized. As new insights into the complex molecular events implicated in growth regulation of the prostate are revealed, the role of the estrogens has become clearer. The present review considers this role in relation to the pathogenesis of prostate cancer and the potential cancer-repressive influence of the dietary estrogens.

**Key words:** chemoprevention, estrogens, phyto-estrogens, prostate.

## Introduction

Estrogens were probably the first compounds to be implicated in carcinogenesis and were also known to suppress cancer growth. Reflecting on attitudes of 50 years ago,[1,2] it was considered that estrogen-related cancer was due, not to a sudden 'over-abundance' of estradiol-17β, but to a long-term supply of relatively small amounts. Males were considered 'more reactive' to estrogens than females, with low concentrations enhancing the effects of androgens in the prostate and inducing aberrant growth. Noteworthy, in 1935, before Doisy had announced the isolation and identification of estradiol-17β, there was speculation[2] that the benign enlargement of the aging human prostate (benign prostatic hyperplasia; BPH) was the consequence of a relative excess of estrogen.

Since then, the role of estradiol-17β in the prostate has been something of an enigma. Once Huggins[3] had established a scientific basis for the treatment of advanced cancer of the prostate by surgical castration, attention was primarily directed either to restraining the intraprostatic action of 5α-dihydrotestosterone (DHT), or alternatively, on lowering plasma testosterone levels. Androgens were recognized as the predominant growth promoting influence on the gland. Today, despite modern biotechnology that has provided a greater understanding of the molecular events implicated in prostatic disease, both BPH and prostate cancer continue to impose worldwide healthcare problems.[4]

Nevertheless, progress can be recognized and with molecular endocrinology well to the foremost, the past decade has revealed an exciting insight into the regulatory processes within the prostate, with its complex intracellular signaling pathways that control growth and function.[5,6] New therapeutic approaches have been conceived[5] and much has been learnt about the clinical management of prostate cancer from a wide range of clinical trials.[7] Important, however, is the continual reassessment of concepts that govern our understanding of treatment strategies and few would deny the controversy[8] throughout this time, on all aspects of this disease, ranging from its natural history, the value of screening for early cancer,[9] to the current interest in chemoprevention,[6] certain aspects of which center on the role of estrogens within the prostate. Prostate cancer can probably be restrained in its latent, indolent form that is so prevalent in men of all ethnic groups, worldwide and the chemopreventive potential of the dietary phyto-estrogens now dominates the media.

The role of estrogens in relation to prostate growth is now seen as more important than hitherto believed, and this review is based on reflections from an International Prostate Health Council (IPHC) Study Group directed to this topic and the clinical value of antiestrogen therapy. Discussion centered on whether phyto-estrogens can restrain prostate cancer progression through their agonistic or antagonistic estrogenic properties, or by some other of the associated imposing range of biological effects (Fig. 1). Benefit may result from their capacity to act as effective antioxidants, as tyrosine kinase inhibitors, or as aromatase inhibitors of estrogen biosynthesis.

## Estrogens and the prostate

Although the male or female phenotype is determined to a large extent by differences in the serum concentrations of the sex steroid hormones, there is no sexual specificity with regard to any particular hormone and there are substantial levels of estrogens in the human male, although markedly less than those of testosterone (Fig. 2). The influence of estrogens on the developing embryonic or neonatal prostate, the impact of the changing hormone balance at puberty and the endocrine status of a young man entering his 20s, together with the more intrusive effects of estrogens on the 'mid-life' prostate, all impinge on growth regulatory mechanisms within the gland. Early estrogen-mediated gene imprinting that can subsequently influence the insulin-like growth factor (IGF)-network, or another of the estradiol-related molecular events in later life, thereby increasing the propensity for prostatic dysfunction, demands fuller investigation.

Substantive evidence for an estrogen receptor (ER) in the canine prostate[10] and the classical studies of Walsh and Coffey[11] which showed that estradiol-17β, together with DHT, or a 5α-androstanediol, induced a fourfold increase in its weight and DNA content, focused attention on their synergistic effects on the gland. Testosterone, together with estradiol-17β, failed to enhance prostate weight. The 5α-androstanediols are weak estrogens[12] that associate with ER. Although there are many recorded effects of estrogen on the prostate,[13] it is the new, elegant type of studies, such as those of Klocker and his colleagues,[14] which will most effectively impact on our understanding the regulatory role of estrogens.

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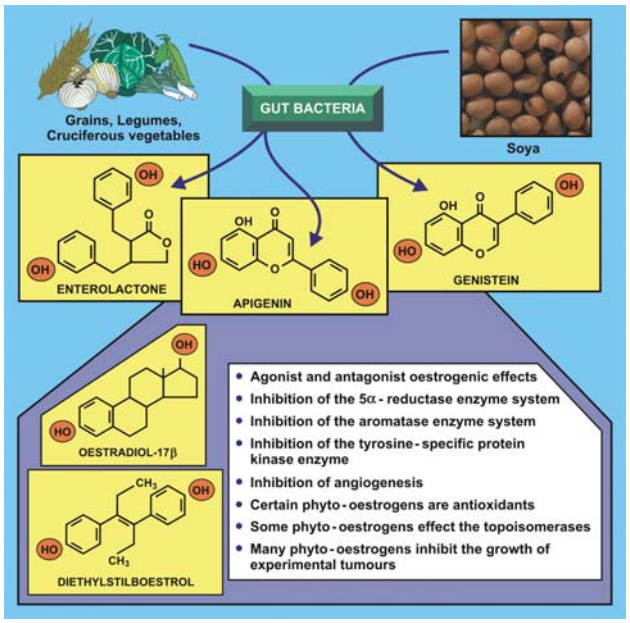


**Fig. 1** Simple portrayal of phyto-estrogen formation from foodstuffs by the gut microflora: some reported biological effects.

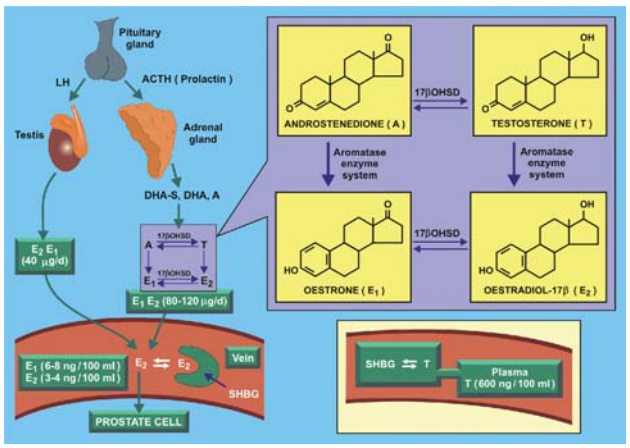


**Fig. 2** Estrogen production in the human male and their concentration in serum relative to those of testosterone. Illustrated is the aromatization of $C_{19}$-steroids by the aromatase enzyme system.

Simply stated, by using gene array analysis and prostate smooth muscle cells in culture, they determined[14] the differential gene expression profile in the presence and absence of estradiol-17β. These identify (Table 1) those genes that are up- or down-regulated. Expression of interleukin 6 (IL-6) and interleukin 8 (IL-8) is down-regulated (Fig. 3), and Table 2 summarizes features of these cytokines which relate to prostate growth regulation. The ras homolog gene family member E (RhoE) is down-regulated (Fig. 4). A member of the Ras superfamily of small G-proteins and intimately concerned in intraprostatic signaling, RhoE is implicated in the regulation of the cytoskeleton, is a potential target for the farnesyltransferase enzymes, and moreover, is a possible antagonist of RhoA, a protein overexpressed in prostate cancer. Expression of RhoE is impaired in human prostate cancer cells. Overexpression of RhoE reduces Du-145 cell growth in culture, inhibiting

**Table 1** Estrogen-regulated genes in the smooth muscle cells of the prostate gland[14]

| Estrogen regulated genes in prostatic smooth muscle cells | |
|---|---|
| Up-regulated genes | Down-regulated genes |
| Amphiregulin | Asparagine synthetase |
| Ankyrin repeat domain 5 | DEAD/H (Asp-Glu-Ala-Asp/His) |
| Cyclin-dependent kinase inhibitor 3 (CDKN 3) | Interleukin 6 (IL-6) |
| A disintegrin and metalloproteinase domain 21 | Interleukin 8 (IL-8) |
| Lipopolysaccharide-binding protein | Methylene tetrahydrofolate dehydrogenase |
| Ran binding protein 17 | Orphan neurotransmitter transporter v7–3 |
| Rela-associated inhibitor | Phosphoserine aminotransferase |
| Serine/threonine kinase 15 | Prostate differentiation factor, plab |
| Solute carrier family 16-member 7 | Ras homolog gene family member E |
| Vanilloid receptor-related osmotically activated channel | Transcription elongation factor A |
| Zinc finger protein 217 | Ubiquitin carboxyl-terminal esterase L1 |
| Zinc finger protein 237 | Serine (or cysteine) proteinase inhibitor (nexin, plasminogen activator inhibitor type 1), serpine |

proliferation (Fig. 5) and inducing apoptosis, possibly by controlling the expression of cyclin $D_2$, a cell cycle regulator.

Such studies emphasize the far ranging influence of estradiol-17β within the complex biology of the prostate and the pathogenesis of prostate disease. This review encompasses four particularly relevant questions (Table 3) raised by Huggins over 40 years ago,[15] for which prevailing concepts that impact on the natural history of prostatic disease (Fig. 6) may now offer an answer.

## The natural history of prostate disease

Prostate cancer develops as a heterogeneous, slowly growing tumor that takes 25 or more years to develop from a focal lesion to the malignant phenotype. Initiation appears to occur soon after puberty and the period of prostate growth. Postpubertal dysfunctional regulatory events, together with a man's inherent sexuality,[16] will play a part in the initiation and development of high-grade prostatic intraepithelial hyperplasia (PIN) and latent focal cancer.

Normally, prostatic homeostasis should be established following puberty, with a balance attained between the rates of cell proliferation and cell death that sustains a growth-quiescent gland despite the high levels of circulating testosterone. Clearly, homeostatic balance is not always established and epithelial hyperplasia can be recognized in the early 20s.

A second fundamental issue is that once prostate cancer is outside the confines of the capsule, the disease is incurable. This clinically aggressive phenotype develops after the age of 50, seemingly supported by endocrine changes associated with the andropause,[17] essentially an increasing estrogen/androgen ratio in serum, resulting from a

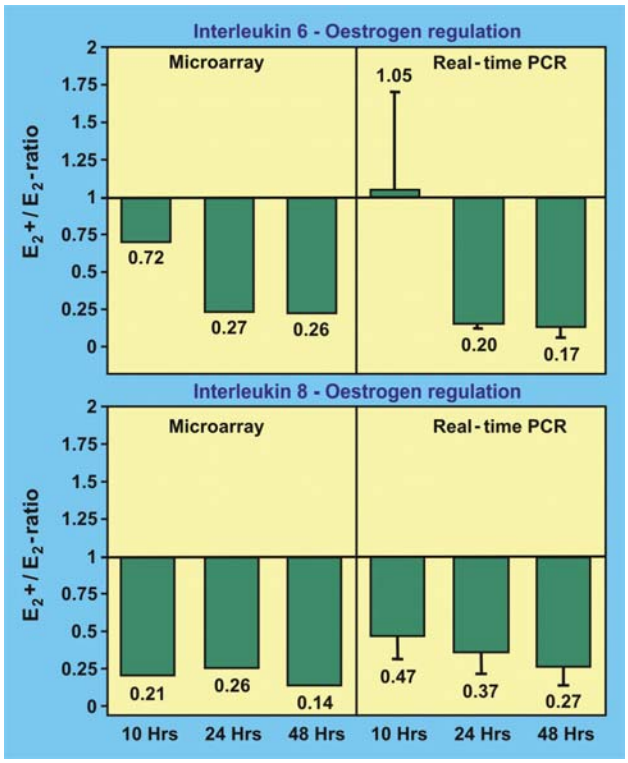


**Fig. 3** Regulation of the interleukin 6 and interleukin 8 genes by estrogen.[14]

**Table 2** Some biological effects of the interleukins 6 and 8

| |
|---|
| Interleukin 6, IL6. |
| Mediator of inflammation and immunological reactions |
| Involved in autocrine and paracrine regulation of prostatic growth |
| May act directly on benign and malignant cells |
| Elevated in the sera of patients with metastatic prostate cancer |
| Regulation by estrogen |
| Interleukin 8 |
| Originally discovered as a monocyte-derived neutrophilchemotactic factor |
| Involved in pathophysiology of BPH |
| FGF-2 up-regulation (r) abnormal proliferation of the prostatic transition zone, angiogenesis |
| Found in various human cancers including prostate cancer |
| Serum concentration correlate with increasing prostate cancer stage |
| Expression correlates with angiogenic, tumorigenic and metastatic potential of prostate cancer |

BPH, benign prostatic hyperplasia.

declining testosterone concentration relative to a sustained level of estradiol-17β. This 'relative estrogen excess', clearly influences the later phases in the natural history of both BPH and cancer, since the incidence of prostatic disease rises exponentially in older men in whom the estrogen/androgen ratio can increase by up to 40%. A simple re-assessment of the natural history of prostate disease, reveals the extent to which estrogens could interfere with these events.

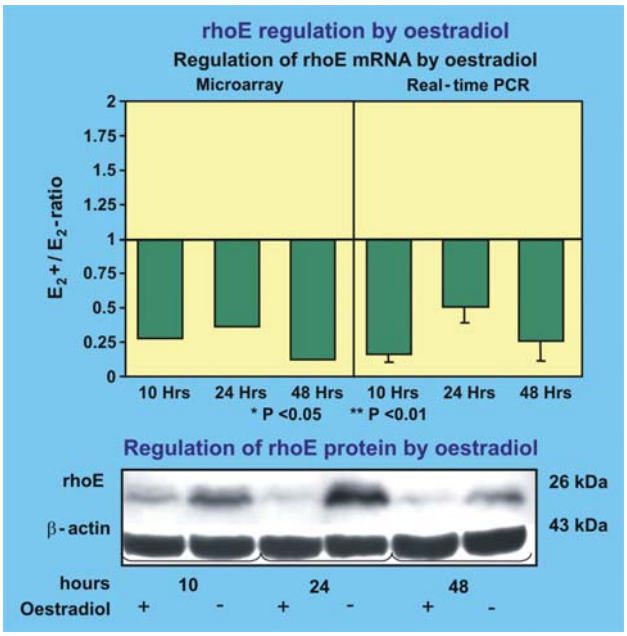


**Fig. 4** Regulation of the rhoE gene by estrogen.[14]

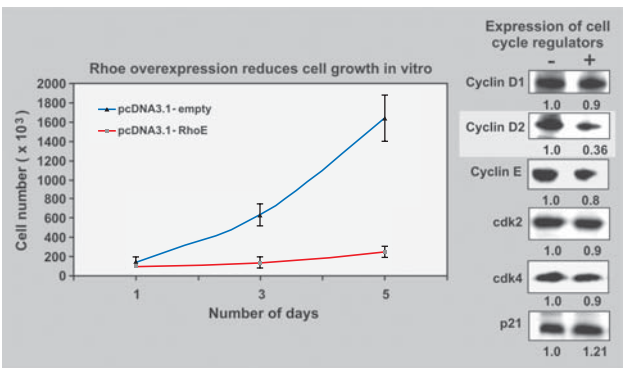


**Fig. 5** Influence of rhoE expression on prostate cell growth.[14]

## Genomic parameters

Cancer is a multistep process involving endocrine, environmental and nutritional factors, as well as the genetic aberrations that promote progressive cellular dysfunction and eventual unrestrained growth. Available evidence suggests there is an all-embracing genetic predisposition to prostate cancer, familial clustering highlighting this and the possibility of cancer susceptibility genes. Segregation analysis,[18] however, reveals that such high penetrance genes are of low frequency, accounting for less than 10% of patients. Linkage studies[19] have mapped hereditary disease to the long arm of chromosome 1, the HPC-1 locus (1q24–25), as well as to other loci, namely PCAP (1q42.2–43), CAPB (1p36), HPCX (Xq27–28) on the long arm of chromosome X and also 16q.

Probably more important, however, are the genetic polymorphisms, point mutations, deletions or insertions of a small number of nucleotides within a DNA sequence, that induce the expression of aberrant mRMA transcripts and particular proteins implicated in disease etiology. Polymorphic variants of low penetrance susceptibility genes, which relate to estrogen and androgen metabolism and their associated

**Table 3** Perceived important issues relating to human prostatic disease in 1962[15]

| | |
|---|---|
| | The geographic difference in prostate cancer incidence. |
| | Prostate cancer is common, but cancer of the seminal vesicles is rare |
| Professor | Cancer and BPH are clinically manifest after 50 years. What is the age factor? |
| Charles Huggins | Prostate cancer is prevalent in African-American males. |

BPH, benign prostatic hyperplasia.

signaling pathways, have been mapped to frequently deleted regions in prostate cancers. For example, the AF-1 transactivation function of the androgen receptor (AR) is located in the N-terminal domain encoded by exon 1 and characterized by polymorphic trinucleotide CAG repeats encoding a polyglutamine track. Depletion of CAG repeats has been related to an elevated AR transactivation activity and higher risk, with a greater prevalence of the shorter alleles in African-Americans and a lower prevalence in Asian men, the difference reflecting the geographic variation in prostate cancer incidence.[20]

The SRD5A2 gene, mapped to 2p22–23, encodes the 5α-reductase type II enzyme. A VL89 mutation reduces its activity, relates to ethnic groups[21] and low serum 5α-androstanediol glucuronide levels, considered a marker of overall DHT production.[22] The 5α-androstanediols assume importance, since 5α-androstane-3β,17β-diol is recognized as a weak estrogen[12] and now identified as a principal estrogen in the mouse prostate.[23] An A49T missense mutation relates to a fivefold increased activity, poor prognosis and risk in African-American men.[24] Aberrations of the HSD17B2 gene, encoding for 17β-hydroxysteroid dehydrogenase type II, concerned with the interconversions of testosterone, androstenedione, estradiol-17β and estrone, could lead to inappropriate endocrine effects in the prostate. African-American men have higher estrogen levels than their European and Japanese counterparts.[22]

As prostate cancer progresses, mutant AR in metastatic tissue can accelerate growth through inappropriate binding of antiandrogens, as well as estrogens, glucocorticoids, progesterone and adrenal androgens.[25] The beneficial response of patients with advanced disease to the withdrawal of flutamide is well documented.

Estrogens appear to be implicated in the complex regulatory events of the cell cycle in the prostate, homeostatic balance normally maintaining a quiescent state. The cellular response to growth promoters such as epidermal growth factor (EGF) involves $G_0$ resting cells entering the $G_1$ phase (Fig. 7), where a progression factor such as IGF-I ensures that the cell is committed to advance into S phase and DNA synthesis. In late $G_1$, growth-restraining factors such as transforming growth factor (TGF)-β, tumor necrosis factor (TNF), or interferon (IF-1), can control events at this decision point, with advancement regulated by signals invoked by cyclin-dependent kinases. Cyclins, which promote, or restrain growth suppressor activity by inducing their phosphorylation, can drive the cell through the cycle. The retinoblastoma (Rb) protein represents a suppressor that provides a cell cycle brake and its activation by cyclin $D_1$-induced phosphorylation removes this braking capacity such that the cell can advance into S phase. Estrogens appear to be intimately concerned with cyclin $D_1$,[26] which inhibits the functional activity of AR. Gene deletion, the loss of Rb, confers a growth advantage to the cancer cell. The p53 protein prevents a damaged cell from proceeding into the cell cycle until DNA repair is complete and loss or inactivation of a p53 gene is generally an event related to the progressive and refractory phases of prostate cancer.

## Estrogenic signals in utero: carcinogenesis and imprinting

That transplacental transmission of an endocrine signal can induce cancer was originally described by Herbst,[27] who reported an uncommon clustering of adenocarcinoma of the vagina in young women, recognized as a consequence of the estrogenic imprinting action of diethylstilboestrol (DES) on embryonic vaginal tissue following its administration for threatened abortion. Others have hypothesised[28] that a similar predisposition to develop breast and prostate cancer occurs through estrogen-mediated embryonic events that in later life, 'trigger' aberrant growth.

Preneoplasia is recognized in the genital tract of offspring of mice to which DES had been administered during gestation.[29] Coffey[30] considers that imprinting promotes an enhanced AR expression in epithelial cells of the adult prostate and Prins[31] identified disturbed TGF-β signaling, with proliferation of periductal fibroblasts. Expression of TGF-$\beta_1$, localized in smooth muscle cells, was enhanced, whereas TGF-$\beta_2$ and TGF-$\beta_3$ expression in differentiating epithelial cells was repressed, 10–30 days after estrogen exposure. The normal transient nuclear localization of p21, the cyclin-dependent kinase inhibitor induced by TGF-$\beta_1$, recognized in epithelial cells between days 6–15 and concerned with differentiation, was also inhibited. Estrogens regulate TGF-$\beta_1$ expression and these elegant studies suggest that the layer of fibroblasts represents a physical barrier that constrains differentiation, inhibiting reciprocal paracrine signaling between stroma and epithelium.

Certain simple, classical aspects of maleness and femaleness may be worth a revisit in relation to the reawakened interest in estrogens in the male. The biology of sexual differentiation was described 30 years ago.[32] Essentially, certain biological steps are required in the process of becoming a male, which are not needed for 'femaleness' to occur. Without them, the newborn tends towards the development of femaleness, or a phenotypic male with certain female characteristics. The male behavioral pattern is induced by androgens within a 24-h period after birth, and castration beyond 24–48 h of neonatal life cannot reverse the process. This early androgen-mediated sexual differentiation of the male brain, with endocrine changes occurring with exquisite timing during development to establish patterns of physiological activity and sexual behavior in later life, will impinge on prostatic development.

Possibly relevant is that a 50% increase in the serum estradiol-17β levels within a male mouse embryo resulted in an enlarged adult prostate gland, with a sixfold higher level of AR,[33] whereas a fivefold pharmacological increase suppressed prostate growth. The prevalence of prostate cancer in African-Americans in relation to the report[34] that African-American mothers have up to 40% higher concentrations of plasma estradiol-17β than their white counterparts, is worthy of comment.

Insights into the molecular events of imprinting indicate that it involves methylation of CpG dinucleotides within regulatory regions of genes such that transcription is inhibited.[35–37] An imprinted gene is therefore inactive, or 'silent', such that the contributions of maternal and paternal genomes may not be functionally identical. For example, after implantation of the blastocyst in the mouse, the IGF-II gene is exclusively expressed by the paternal allele, whereas the

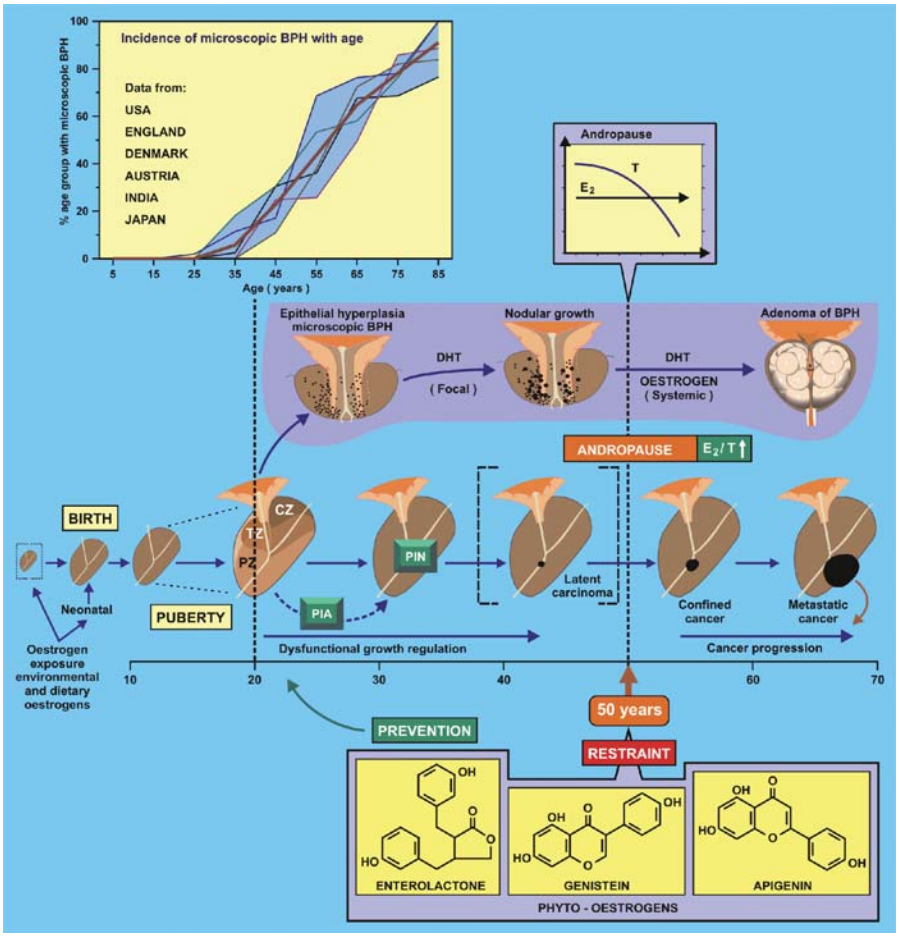


**Fig. 6** Diagrammatic representation of the natural history of prostate disease, illustrating the slow-growing nature of prostate cancer.

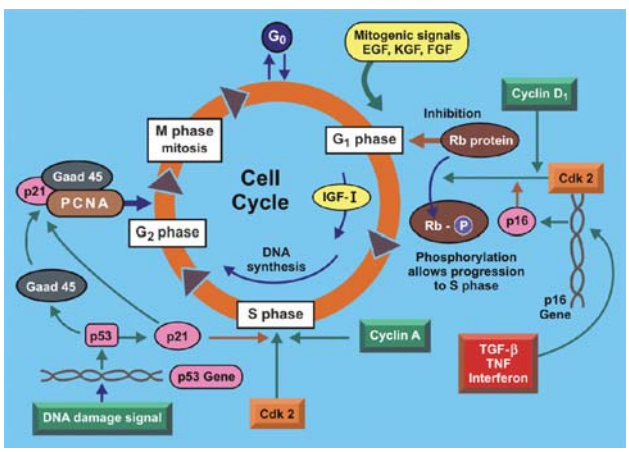


**Fig. 7** A simplified illustration of the role of some of the factors that regulate the cell growth cycle within the prostate.

corresponding maternal allele is silent. Biallelic expression may occur later in development.[36] Newly recruited transcription factors introduced at discrete periods during prostate growth can influence subsequent gene activity.

Imprinting is implicated in early stages of carcinogenesis[38] and removal of an imprint, an inability of preneoplastic cells to respond to an imprint, or variability in the availability of other particular time- and tissue-specific regulatory transcription factors that might normally maintain the silence of an imprint and thereby influence DNA methyltransferases, may occur. Whether a gene concerned with the IGF-signaling network, or another related to steroid-mediated signaling, provides the adverse stimulus to cell proliferation, remains to be determined.

## Adolescence, puberty and sexuality

Since androgens are seen as the major driving force in the development of the mature male and his prostate, it is not unreasonable that male sexuality could be considered to exercise an over-riding influence on the gland.[16] The precise relationship remains equivocal, possibly because of understandable difficulties in obtaining honest, reliable data on sexual activity from the average male. Rotkin[16] suggested that such variable endogenous factors would influence the natural history of prostate disease. Rotkin considered the unfulfilled coitus of a shy personality could invoke certain adverse events within the prostate and reported that patients with prostate cancer masturbated less and had less coital activity than control males, generally experiencing less frequent ejaculation.

The physiological balance between a male's androgen and estrogen levels could impinge on these events, especially since estrogens are intimately involved in male puberty. Estrogens enhance the secretion of prolactin, which is implicated in the synthesis of the adrenal androgens at adrenarche.[39] Prolactin influences prostate growth, localizing to epithelial cells and increasing cell proliferation in BPH tissue explants in

culture.[40] Transgenic mice over-expressing the rat PLN gene develop a dramatic prostate enlargement that resembles BPH.[41] A high fat intake elevates serum prolactin and the reported suppression of the normally elevated nocturnal levels of plasma prolactin in those who change from an omnivorous to a vegetarian diet,[39] emphasizes the close relationship between estrogens, prolactin and diet.

Growth hormone (GH) and consequently, the IGF-network, are also intimately involved in adolescence and puberty, with GH and IGF-I secretion promoted by estrogens. IGF-I mediated signaling induces epithelial[42] and stromal cell[43] proliferation, and systemic administration of IGF-I, but not EGF, promoted growth of the rat prostate.[44] Moreover, serum IGF-I levels increase during early puberty,[45] promoting LH-RH release from the hypothalamus. IGF-I administration will advance the stages of puberty. Enhanced expression of the IGF-I gene was identified[46] in the liver of rats during puberty, with a corresponding rise in serum IGF-I and gonadotrophin levels, an associated enhancement of IGF-IR in the median eminence, release of LH-RH and activation of the pituitary–testicular–prostatic axis.

The role of IGF-I in prostate growth regulation assumes greater importance.[47] An incompletely developed prostate was identified in IGF-I deficient transgenic mice[48] and elevated levels of IGF-I appear to predict prostate cancer risk, with the ratio of IGF-I/IGFBP-3 in serum particularly significant.[49] Interestingly, in China where the incidence of prostate cancer is low, but the prevalence of BPH similar to that in the West, a case–control study showed that BPH is positively associated with plasma IGF-I levels and inversely with IGFBP-3.[50] Serum IGF-1 levels in subjects with evidence of PIN, as well as those with prostate cancer were higher than controls.[51] Estradiol-17β enhances the expression of GH-receptor in the liver and this relates to IGF-I expression.[52] Patients with acromegaly have a high prevalence of prostate enlargement that is associated with elevated plasma levels of GH and IGF-I and reduced circulating androgen levels.[53] Severe insulin resistance is also characteristic of acromegalics, who have a propensity to develop cancer, particularly of breast.[53,54] Possibly relevant, is that tamoxifen decreases levels of serum IGF-I in patients with breast cancer[55] and influences the IGF-I/IGFBP-3 ratio to favor the growth inhibitory actions of IGFBP-3. The phyto-estrogens genistein and daidzein may well beneficially influence male puberty. A Western diet lowers the age of menarche – there are marked differences in the onset of hormone secretion and ovulatory cycles between girls in Britain and Thailand[56,57] – and may influence the LH-RH pulse generator in males.

The foregoing highlights particular aspects of puberty that involve estrogens. Classically, it is considered[58] that the onset of puberty is 'physiologically gated', governed by the energy resources of the body, especially in the female. The discovery of leptin, the antiobesity protein, provided another important insight into the 'endocrine puzzle' of puberty.[59] The obesity (Ob) gene is exclusively expressed by adipocytes and the action of leptin on the neuroendocrine–reproductive axis that induces the onset of puberty, probably exercises a permissive role as a 'metabolic gate'. Leptin now assumes an important neuroendocrine role and as Professor Robert Steiner stated,[60] 'The story of leptin has all the earmarks of a Dostoyevsky novel: you know it is bound to get more complicated before it ends with some great Truth'. Studies on leptin have centered on the female and emerging results demonstrate racial differences in levels of plasma leptin and in its role in controlling resting energy expenditure between black and white women, differences that may be concerned in the prevalence of obesity in the African-American population. A relationship to adverse risks with regard to prostatic cancer will undoubtedly invoke controversy. The consequences of Ob gene mutations, or in the leptin receptor (Ob-R), with ineffective signaling in the hypothalamus that delays or impairs the complex processes of puberty, require consideration.

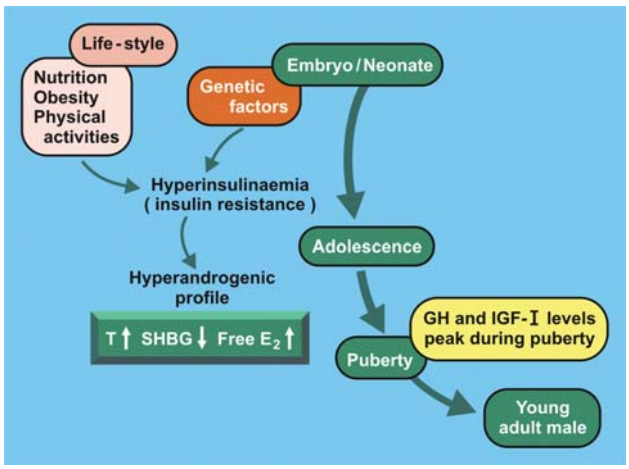


**Fig. 8** Potential influence of insulin resistance on the development of a hyperandrogenic status in the younger mature male.

Such genetic factors may well determine any predisposition to obesity, influencing body fat distribution and promoting some degree of insulin resistance.[61] Preadolescent nutrition, associated obesity and limited physical activity, could be the environmental factors that invoke hyperinsulinemia and endocrine dysfunction. Hyperinsulinemia promotes a hyperandrogenic status, with elevated plasma testosterone and free estradiol-17β levels associated with reduced sex hormone binding globulin (SHBG).[62] Insulin is a principal regulatory factor that inhibits SHBG synthesis by the liver and lower SHBG levels would be consistent with a higher prostate volume.

Kaaks[61] suggests that this hyperandrogenic profile in association with insulin resistance constitutes a risk factor for breast cancer (Fig. 8). A Finnish study[63] indicated that preadolescent hyperandrogenicity persists at least 12 years after puberty. Interesting therefore is whether a certain degree of insulin resistance in the male early life contributes to the development of a hyperandrogenic endocrine-metabolic profile that is associated with the early premalignant lesions in the prostate and a greater risk of malignant cancer.

## The natural history of benign prostatic hyperplasia

Early epithelial cell hyperplasia, which can be recognized in the periurethral region of the prostate during the early 20s, often culminates in the extensive stromal cell hyperplasia and stromal adenoma associated with bladder outflow obstruction (Fig. 8) prevalent in men beyond the age of 50, and an inappropriate estrogenic influence at 'mid-life' has long been considered responsible for the stromal cell proliferation.[64] The andropause relates to a period in life when plasma testosterone levels generally fall due to declining testicular function (Fig. 9). The concentrations of estradiol-17β are sustained, however, due to the aromatase activity of adipose and muscle tissue, converting adrenal androgens to estrogens. This estradiol-17β imbalance at the andropause[17] is widely accepted as a principal cause of stromal hyperplasia and prostate enlargement.

Microscopic foci of prostate epithelial hyperplasia can be recognized in men as early as 25–30 years of age[65] and, moreover, in men, from East and West (Fig. 6), the prevalence increases with age. This

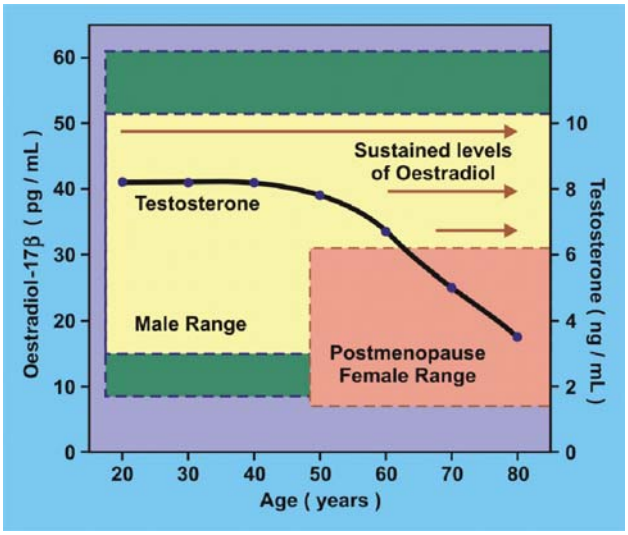


**Fig. 9** Some endocrine changes during the male andropause.

'microscopic BPH' develops into nodules, primarily glandular hyperplasia, localized in the transition zone and periurethral tissue, which begin as a cluster of new, glandular epithelial branches, budding eccentrically from the wall of a duct,[66] with the stroma implicated as a source of growth factors.[64,67] This random focal development of nodules suggests a locally regulated process, promoted by androgens,[25] whereas clinical BPH is seen as a consequence of the enhanced estrogenic status of the older male, benign adenomatous enlargement most often being composed of stromal elements, primarily muscle tissue.[68]

## Prostatic intraepithelial neoplasia

Substantive evidence indicates that high grade PIN, located in the peripheral zone of the human prostate, is an early premalignant lesion.[69,70] PIN is recognized in a high proportion of samples of prostatic tissue containing cancer, and a continuum of genotypic and phenotypic characteristics can be recognized, from benign prostate glands, through low and high grade PIN, to the aggressive cancer phenotype. PIN is characterized by strong immunochemical evidence of epithelial AR and various growth factors,[71,72] with enhanced expression of EGF-R and TGF-α. EGF or TGF-α mediated cell proliferation requires EGF-R to trigger intracellular signaling[73] and their expression highlights a pivotal role in the high grade PIN and prostate cancer, proliferation being higher in high grade PIN than in PIN or BPH tissue. PIN therefore represents a precancerous lesion that can progress to foci of latent cancer and ultimately, to the malignant cancer phenotype.

## Latent cancer of the prostate

The slowly growing, indolent latent carcinoma of the prostate, an intraprostatic microscopic foci of well differentiated cancer cells, is comparatively common in men of all ethnic groups worldwide, just as prevalent in Japanese males as in Caucasians of a similar age.[74] Smaller foci are found in a substantial proportion of prostates from men, worldwide, whereas the prevalence of larger foci follow a geographic variation, similar to that for clinical cancer, essentially a higher prevalence in the West. Studies[75,76] of males between 10 and 50 years of age, reveal that microfoci of cancer were present in the prostates of nearly 30% of

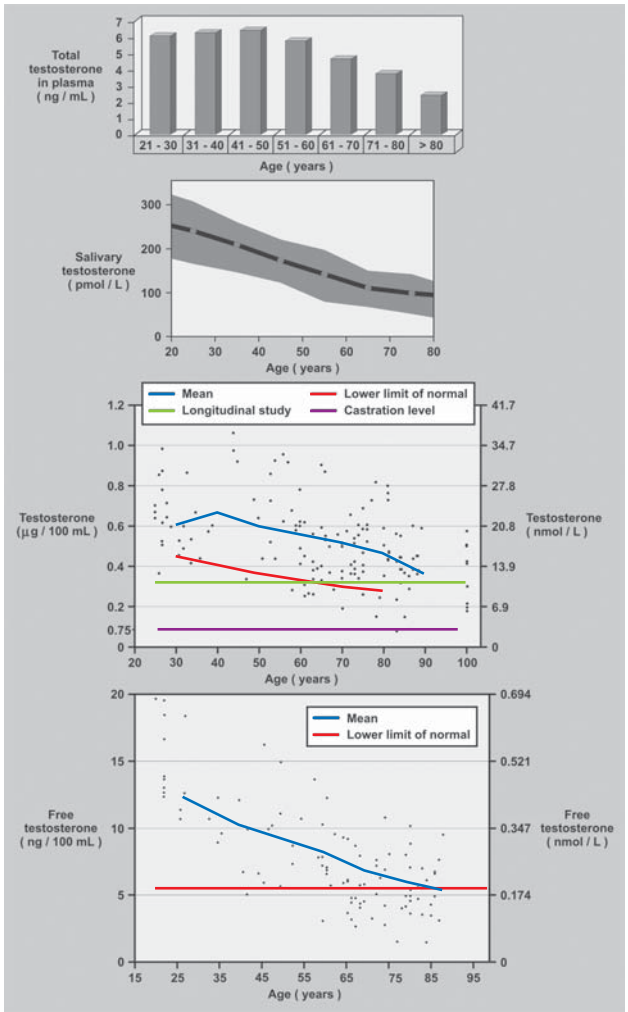


**Fig. 10** Changes in plasma and salivary testosterone with increasing age.[6]

men between 30 and 40 years of age, sustaining the concept that prostate cancer initiation occurs in the immediate postpubertal years, in males of all ethnic groups.

The worldwide prevalence of latent prostate cancer, relative to the marked geographic variation in clinical disease, again focuses attention on the age factor, the andropause[17] and the question as to whether estradiol-17β is implicated in prostate cancer progression. Compelling evidence certainly supports the concept that certain dietary constituents of the Asian diet can protect against progression.[6] There appears to be a pivotal role for estrogens at this phase of life in the development of prostate disease. Serum testosterone levels fall,[17,77] (Fig. 10), whereas estradiol-17β concentrations are sustained, albeit, over a wide range, sometimes twice those of the postmenopausal female. It must be recognized that estradiol-17β acts at very low biological concentrations and it remains to determined whether such individual differences are important to progression.

Apart from certain reported major ethnic differences,[78] classical hormone analysis has rarely provided any unequivocal information with regard to the etiology of prostate disease in an individual, although low serum testosterone and high GH concentrations can be identified in patients presenting with poorly differentiated cancer of the prostate.[79]

With regard to familial clustering of cancer of the prostate,[80] patients and their first-degree relatives had lower plasma levels of testosterone than matched controls and a greater capacity to synthesize estrogens. There are certain trends, with lower concentrations of plasma testosterone and estradiol-17β found in Japanese men, compared to their western counterparts.[78]

## Prostatitis: proliferative inflammatory atrophy

Coffey's fascinating studies showed that estrogen imprinting induced an inflammatory reaction in the rodent prostate.[13] Moreover, a spontaneous inflammatory response was seen in animals on a soy-free diet, a lesion prevented by increasing soy intake and levels of plasma genistein.

Estrogens implicated in the induction of inflammatory disease of the rat prostate and a recent provocative concept[81,82] suggests that the inflammatory reaction within the human prostate that is associated with prostatitis, or severe pelvic pain syndrome, may constitute a preneoplastic condition. Patients often present with this disorder in their early 30s, suffering from a range of diverse symptoms that include bacterial infection, lower urinary tract problems, severe pelvic pain, inflammation, sexual dysfunction and importantly, with an impaired quality of life. Also prevalent are anxiety, depression and an impairment of intimate sexual relations, problems not unusually leading to sexual dysfunction.

The diverse facets of this multifactorial disease therefore impact on sexuality, and involve dysfunctional cellular pathology and invading uropathogens, as well as the inflammatory response. The inherent molecular endocrinology associated with inflammation, not only provides new innovative approaches to treatment,[83] but insights into possible interrelationships with other dysfunctional states of the prostate, essentially a transition between the lesion, now referred to as proliferative inflammatory atrophy (PIA)[81,82] and high grade PIN.[84,85]

Areas of prostatic inflammation are specifically associated with the disruption of the secretory epithelial cells. Contemporaneously, the associated damage and atrophy of the epithelial elements promotes a complementary cellular proliferation. Certain pathogens have been identified in prostate tissue, while other uropathogens await identification in relation to the inflammatory 'non-bacterial' chronic prostatitis.[86] It is noteworthy that, as well as estrogens, TNF[83] and IGF-I are also implicated in the biological processes that induce the inflammatory response.[86]

Classically, Franks described a particular type of focal atrophy of the prostate that he considered secondary to aging and a precancerous lesion, with the atrophy often being associated with lymphocytic infiltration.[87] Areas of proliferation then developed from this atrophic epithelium, a pattern considered to resemble the structure of small acinar carcinoma. McNeal,[87] however, considered the epithelial atrophy was secondary to 'an inflammatory process' and that cancer develops within hyperactive glandular epithelium, by way of a slow, gradual process. The contemporary viewpoint of De Marzo[81,82] now re-emphasizes the concept that the diffuse atrophy induced by androgen withdrawal is quite distinct from the focal atrophy associated with inflammation and the complementary cellular proliferation characteristic of the lesion.

The proposed relationship between inflammation and cancer is not unreasonable. Inflammatory lesions generate free radicals including nitric oxide and highly reactive species of oxygen that can be toxic; the hyperactive state and a capacity to cause DNA damage allows free radicals to induce precancerous changes.[88] Macrophage and neutrophil

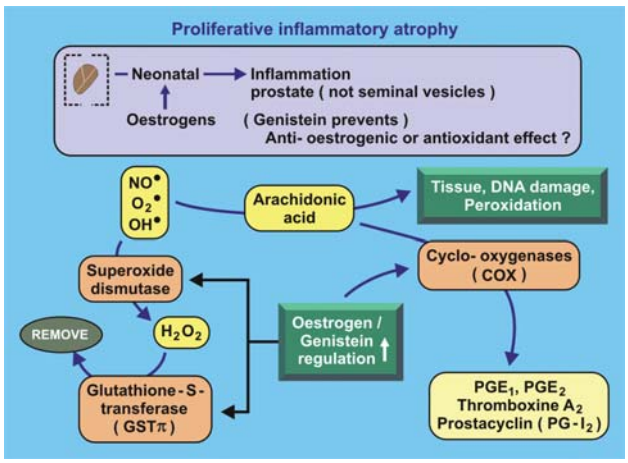


**Fig. 11** Some molecular relationships relating to proliferative inflammatory atrophy.

infiltration to the lesion provides a source of such reactive oxygen species, normally removed by the superoxide dismutase enzyme, which transforms them into hydrogen peroxide (Fig. 11). This is subsequently removed by specific 'protective' enzyme systems, either glutathione-S-transferase π (GSTπ), or a glutathione peroxidase,[13] enzymes that are catalyzed by the trace metal, selenium.

Such oxidative damage to DNA has been associated with the development of prostate cancer.[13] Moreover, free oxygen radicals also support the production of arachidonic acid, which induces peroxidative changes in vascular tissue that lead to vascular disease. Oxidation of arachidonic acid by the cyclo-oxygenases (COX enzymes), up-regulated in PIA, but not prostate cancer,[89] also releases free radicals and induces specific leukotrienes and prostaglandins-$E_1$ and -$E_2$ during the inflammatory response. The prostaglandins encourage leukocyte infiltration into the inflammatory region and enhance pain receptor sensitivity. Interleukin-1 (IL-1) and IL-8 A induce the specific expression of the COX-2 isoform in proliferating atrophic epithelium.[81,90]

The chemopreventive potential of non-steroidal anti-inflammatory drugs, specific COX-inhibitors, is now being tested against prostate cancer, a strategy directed to the restraint of cyclo-oxygenase activity and thereby, prostaglandin production. Moreover, genistein, as well as many of the ubiquitous array of dietary flavonoids, such as quercetin and apigenin, are very effective antioxidants,[6] that can inhibit cyclo-oxygenases and enhance GSTπ activity. Their cancer preventative properties may well relate, at least in part, to their capacity to restrain the inflammatory response in the prostate by up-regulating GSTπ and repressing COX-2 enzymes.[13] Coffey has often stated that an inflammatory lesion is rarely seen in human seminal vesicles, which correspondingly, rarely develop cancer.[13]

The fascinating molecular events relating to the inflammatory process constitute a defensive mechanism. GSTπ expression, which is promoted by estrogens through ERβ,[91] is up-regulated in PIA, a defensive response in order to restrain the oxidative stress. Genistein's protective action is presumably elicited in a like manner, through ERβ. Particularly relevant with regard to the putative estrogen-mediated progression of prostate disease, is that gene silencing, or imprinting, the aberrant methylation of CpG islands of regulatory nucleotide sequences of the gene that encodes GSTπ, is the most prevalent somatic genomic change identified in prostate cancers.[92,93] Lee and colleagues[94]

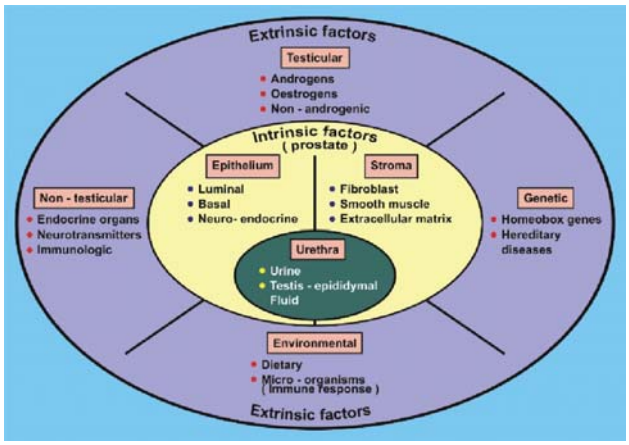


**Fig. 12** Some extrinsic and intrinsic factors that influence prostatic growth and function.

identified GSTπ methylation in nearly 70% of PIN lesions and in more than 90% of carcinomas, but in neither BPH, nor normal prostate tissue.

This common epigenetic event, the loss of the protective GSTπ enzyme, could well be implicated in the proposed transition from PIA to PIN, providing not only a specific growth advantage, but the possibility that estrogens could play a significant role in this transitional step in prostate carcinogenesis. Dysfunctional gene methylation is becoming a common feature of prostate cancer, with aberrant methylation of the A isoform of the ras association domain family protein 1 (RASSF1A) gene, also prevalent in prostatic cancer.[95] The silencing of either of the ERα and ERβ genes, also a common characteristic of prostate cancer[96,97] will influence disease progression. Although ERβ is expressed together with ERα in the normal prostate, it is rarely identified in prostate cancer, emphasizing the possible importance of its regulatory growth-restraining role. Furthermore, the expression of a deletion ER-variants in prostate cancer also highlights the pivotal role of dysfunctional ER-signaling in the progression of the disease to the malignant phenotype.

## Stromal–epithelial interactions

The sophisticated recombinant studies of Cunha[67,98] firmly established that the stroma is a primary target for DHT, modulating its production of growth factors. Nonetheless, although the development of the prostate is absolutely dependent on androgens, it is also a target organ for estrogens, clearly assuming a precise role in growth regulatory events alongside the range of extrinsic and intrinsic factors (Fig. 12) that influence the gland.[64] Very simply, steroid hormones modulate the expression and biological effects of the growth regulatory factors, with the close reciprocal interaction between the stromal and epithelial compartments, recognized as pivotal to growth control.[64]

The AR- and ER-mediated signaling within the stroma promote the expression of growth factors such as KGF (FGF-7) and FGF-2, the former exercising paracrine effects on the epithelium, the latter, an autocrine influence on the stroma. The AR-mediated production of KGF and FGF-10[99] maintain a highly differentiated, non-proliferative quiescent secretory epithelium. The reciprocal stromal–epithelial interactions allow the epithelium to induce stromal smooth muscle cell differentiation.

ERα is primarily localized within the stroma and it has been well accepted[64] that stromal hyperplasia is promoted by estradiol-17β, synergistically with DHT, through FGF-2 expression. The biological effects of FGF-2 are mediated by the FGF-$R_1$, a receptor, expressed by normal stromal cells, that specifically binds FGF-2. The epithelial cells express a splice variant of the FGF-$R_2$, the FGF-$R_2$exonIIb receptor that specifically associates with KGF (FGF-7) to regulate their normal proliferation and differentiation.[64]

Studies of Krieg[100] strongly support the concept that the age-related changes in the metabolism of androgens and estrogens is responsible for the stromal cell hyperplasia associated with BPH. Stromal concentrations of estradiol-17β and estrone increase with age, whereas those in epithelial tissue remain constant. The overall picture portrays an enhanced estrogenic influence, relative to that of DHT, that markedly influences the prostate of the elderly man. An age-related decrease in DHT levels in the transition zone (TZ) of the human prostate, with a resultant enhanced estrogen/androgen ratio,[101] also supports the concept.

Cunha[67] unraveled much of the complexity of the stromal–epithelial interactions. The use of recombinants of mesenchyme and epithelial tissue, grafted to the kidney of host mice, has identified the events by which each tissue regulates the other to sustain homeostatic balance. Moreover, the stromal 'microenvironment' was recognized as a critical determinant of benign, or malignant growth.[67,102] Benign human prostatic epithelium and rat urogenital mesenchyme, grafted as recombinants into host mice treated with testosterone and estradiol-17β, developed invasive carcinoma. Only the mesenchyme had AR and ER.[103,104] Dysfunctional stromal signaling supports carcinogenesis, as 'cancer associated fibroblasts' replace the periepithelial smooth muscle cells and the stroma fails to restrain epithelial cell proliferation.[105] Speculation exists as to whether epithelial cells associated with preneoplastic lesions, or possible microfoci of latent cancer, probably genetically modified but not cancer, influence the stroma to repress its reciprocal restraining action. Stromal changes induce the influx of inflammatory cells, mast cells and neutrophils, which express free radicals and cytokines that also influence epithelial cell proliferation. COX-2 expression is enhanced. Complementary investigations with Dunning tumor systems and TRAMP cancer models[106] suggest that the normal paracrine influence of FGF-7 and FGF-10 on the epithelial cells switches during carcinogenesis to an autocrine mode, whereby the FGFRiiic isoform replaces FGFRiiib, the former preferentially binding FGF-2.[67,107] Contemporaneously, the epithelial cells express FGF-2, with progression to malignancy. In the TRAMP model, the epithelial FGFRiiib receptor is replaced by FGFR1 normally expressed specifically by the stroma. Such studies forcefully direct attention to dysfunctional signaling by the prostatic FGF-network, possibly implicating aberrant ER and AR regulation.

## Some molecular aspects of estrogen action in the prostate

An exciting development of the past decade was the identification of a second ER, referred to as ERβ,[108] with a high affinity for estradiol-17β and moreover, expressed in prostate epithelium. The discovery invoked fresh interest in the role of estrogens within the gland and the precise function of ERβ-mediated signaling pathways relative to those controlled by ERα. ERα and ERβ have functional similarities with regard to their binding affinity for estradiol–17β and their association with genomic recognition sites, as either homodimers or heterodimers,[109] but it seems that their specific roles can be quite distinct, sometimes complementary, but often antagonistic.

In the mouse ventral prostate, molecular events mediated by ERβ are clearly important, the majority of epithelial nuclei express the receptor and in βERKO mice, all these cells are in the cell cycle, not in $G_0$. AR levels are elevated and the gland contains areas of hyperplasia,[110] with most epithelial cells expressing Ki-67. Moreover, prostatic hyperplasia progressively develops as BERKO mice age, with PIN lesions identified in later life.

In the human prostate, epithelial elements would seem a target of ERβ-mediated estrogen signaling and loss of the receptor in PIN lesions supports its regulatory, role in repressing cellular proliferation. The absence of the ERβ gene allows the accumulation of cells normally programmed to die. ERβ regulates cellular proliferation by suppressing estrogen-mediated ERα-signaling pathways that promote AR synthesis.[111] ERβ preferentially binds genistein, which has also been shown to suppress AR expression.[112] Such studies provide a new insight into the estrogen conundrum. Estradiol-17β can therefore exercise divergent effects, in part through AR expression, depending on the cellular content of ERα and ERβ. Genistein, presumably through ERβ, similarly induces G2M phase cell cycle arrest and cellular apoptosis, an effect associated with p53-independent up-regulation of p21 expression and the down-regulation of cyclin B1.[113]

The antiestrogen tamoxifen also induces p21 expression and S-phase cell cycle arrest in Du145 and PC3 prostate cancer cells.[114] Also noteworthy is that 5α-androstane-3β,17β-diol elicits an estrogenic response in the aorta, but not the pituitary, and associates with ERβ to decrease AR content in the wild-type prostate, but not in BERKO mice.[23]

The estrogen conundrum remains complex, however, as evidence emerges of various splice variants of ERβ, now recognized as $ERβ_1$. $ERβ_2$ has a 1000-fold lower affinity for estradiol-17β, $ERβ_{cx}$ has no affinity and ERβs 3–5, all ER-subtypes, can form heterodimer complexes and thereby influence ER-signaling. The interrelationships of the ER-subtypes to the various coregulators that control transcription, activators, repressors and integrators,[115,116] that form bridges between receptors and ligands on the genome, remain to be determined.

Estradiol-17β mediated signaling through either ERα or ERβ, can elicit differential activation at AP-1 sites and thereby, opposing biological actions. Although the estrogen and DNA binding domains of ERα and ERβ are similar, such that they bind to the same genomic ERE, the N-terminal A/B region of the receptor and its associated transcriptional activation function (AF-1) are different. ERα and ERβ can therefore exercise differential gene expression through receptor protein–protein interaction with other transcription factors associated with the DNA. Tamoxifen can therefore positively promote transcription through ERβ-mediated signaling, an action that would tend to explain its estrogen agonistic effect on the uterus and through ERα and AP-1 sites, its antagonistic influence on breast cancer.

Important then, is whether estradiol-17β mediated intraprostatic signaling assumes greater importance, if the activity of the DHT signaling pathway is impaired by declining plasma testosterone levels at the andropause, an effect that could impact on a prostate gland harboring a latent cancer. If differential expression of ERs is implicated in disease progression, therapeutic strategies to oppose these events could offer an innovative new approach to patient management.

## Antiestrogen action: the potential of selective estrogen receptor modulators

Discussion now centers on strategies directed to the clinical efficacy of antiestrogen therapy. The potential of selective estrogen receptor modulators (SERMS) is evident and these, together with aromatase inhibitors and the innovative Mepartricin, the former inhibiting aromatization in adipose tissue, the latter lowering serum estrogen levels by interfering with steroid enterohepatic recirculation, could offer different options for the management of prostatic disease.

The steroid-binding domain of ERα consists of an antiparallel α-helical sandwich containing 12 α-helices and a 'protected' steroid binding pocket.[117,118] With estradiol-17β bound into a pocket within the estradiol-ER-complex, a short amphipathic α-helix in the C-terminal region of the steroid binding domain, controls AF-2 activity. This helix 12 locks the cavity and folds the domain into a transcriptionally competent AF-2 configuration. As such, the complex can then interact with the specific coactivators, corepressors and integrators necessary for effective gene activation and expression. The binding of tamoxifen induces a different configuration in relation to helix 12, such that the AF-2 is transcriptionally incompetent and coactivators cannot be recruited, thereby inhibiting ER-mediated transactivation.

Various growth factor signaling pathways that induce downstream MAP-kinase phosphorylation, can also induce transcriptional activation of ER in the absence of steroid ligand.[119–121] Briefly, ER-mediated signaling by receptor transactivation, can be promoted by growth factors such as EGF, TGF-α or IGF-I in the absence of estrogen. Particularly important, however, is the role and recruitment of the AR coregulators in the growth regulatory processes of the prostate. The interrelationship between receptors and coregulators is complex, with coactivators, corepressors and intergrators influencing gene transcription by acting as a 'bridge' between the steroid receptor and the transcriptional factor complex.[122] Important, with regard to the putative influence of estradiol-17β on progression, is the interaction between the ERs and the cell-specific coregulators on the genome of prostate cancer cells, an interaction that could be different not only for ERα relative to ERβ, but also for the various ER subtypes.

Seemingly exciting with regard to estrogen action in the prostate is the AR coregulator, $ARA_{70}$, a relatively specific coactivator of AR.[123] $ARA_{70}$ enhanced transcriptional activity of mutant AR in the presence of DHT, but also important is that it induced AR transcriptional activity more than 30-fold in the presence of estradiol-17β, but not DES. The effect was reported to be estradiol-17β specific and dose-dependent at physiological levels. Estradiol-17β may therefore have a more direct role in AR-mediated signaling. Although mutant AR offer an explanation as to how estrogens could sustain prostate cancer progression and prostate-specific antigen (PSA) secretion, it appears that estradiol-17β can also activate AR target genes such as the PSA gene, in the presence of AR and its coactivator, $ARA_{70}$. If estradiol-17β is implicated in prostate cancer progression, then the observed effect of DES on the interactions of these 'tripartite receptor complexes',[122] provides support for the use of DES, or possibly antiestrogens, as a therapeutic option for progressive advanced cancer of the prostate.

Selective estrogen receptor modulators elicit antagonist and agonist effects, depending on specific tissue characteristics and the interaction between the SERM and the available ER subtypes that are expressed. The possibility that specifically designed SERMS could be synthesized with specific antagonistic effects through ERβ mediated signaling, will undoubtedly constitute a new and exciting approach to therapy.[124] Essentially and pragmatically, an effective SERM will do the work that genistein may well do and has done for the Asian people through the years.

## Antiestrogen therapy: the potential of mepartricin

Fiber intake has long been considered a health benefit, the fiber profoundly affecting the enterohepatic circulation of estrogens, a larger

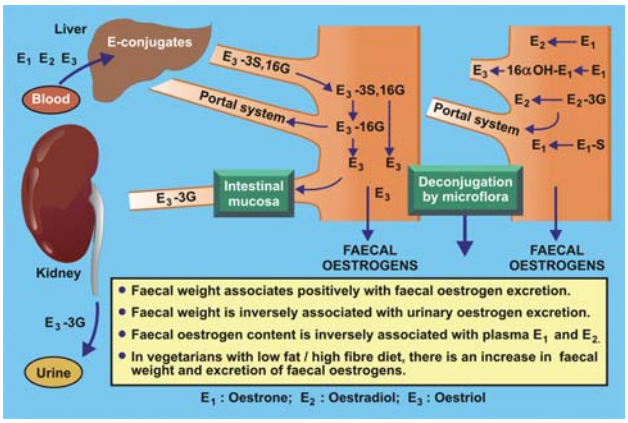


**Fig. 13** The influence of a high fiber diet and of Mepartricin, on estrogen excretion.

fiber intake with greater fecal output increases[125] the fecal excretion of estrogens. This is associated with a decreased urinary excretion of estrogens, an increased fecal estrogen excretion and a lower concentration of estrogens in plasma. Similarly, high fiber intake lowers plasma levels of estradiol-17β and testosterone.[126]

In relation to this, a new approach, to managing prostate disease, particularly BPH, is the use of Mepartricin (SPA: Società Prodotti Antibiotici S.p.A., Milan), marketed under the trade name Ipertrofan. A semisynthetic derivative of a polyene antibiotic isolated from a *Streptomyces aureofaciens* culture, in doses used clinically, Mepartricin is not systemically absorbed after oral administration and is well tolerated. It irreversibly binds estrogens within the gut[127] and interferes with the enterohepatic system that would normally promote their re-absorption (Fig. 13). In a manner similar to that of vegetarians on a high fiber diet, there is a consequent increased excretion of fecal estrogens in the form of Mepartricin-steroid complexes and decreased plasma concentrations of estrogens through the interruption of the enterohepatic recirculation.[128,129]

Mepartricin administration to rats suppresses prostate ER levels and also in prostate tissue of dogs with spontaneous prostatic hypertrophy.[129] In a concentration-dependent manner, Mepartricin restrained the passage of estrogens through the intestinal wall.[130] Its capacity to exercise antiestrogen-like effects was seen in castrated rats treated with estradiol-17β, in which Mepartricin inhibited the estrogen-induced increase in weight of the dorsal lobe of the rat prostate gland.

In a multicenter, double blind, randomized, placebo-controlled clinical trial of Mepartricin for the treatment of symptomatic BPH, patients were randomly allocated to a 24-week treatment period with either Mepartricin (40 mg daily), or placebo. There was a 2-week placebo run-in period. The patient inclusion data, together with the primary and secondary criteria of efficacy, are presented in Table 4. There was strong evidence of a more rapid and significant ($P = 0.006$) decline in the mean I-PSS of patients treated with Mepartricin than in controls (Fig. 14). The mean increase in maximum flow rate (mL/s) of treated patients relative to controls and determined at 6 months (Fig. 15), showed a significantly different ($P = 0.053$) linear trend between the groups. Figure 15 illustrates the benefit of Mepartricin with regard to the improvement in the Quality of Life index evaluated at baseline and after 6 months treatment.

The tolerability issues and clinical efficacy data, that relates to declining serum concentrations of estrogens and significant symptomatic improvement in patients with BPH, illustrates the potential value of this simple and seemingly effective form of therapy that offers a new approach to the management of BPH, possibly of prostatitis[131] and a possible approach to the restraint of prostate cancer progression.

**Table 4** Patient entry criteria and primary and secondary evaluation of Mepartricin efficacy

| |
|---|
| Main inclusion criteria |
| Age between 55 and 80 years. |
| Newly diagnosed BPH. |
| Moderate prostate symptom score (I-PSS between 12 and 24). |
| Post voiding residual urine <100 mL. |
| Urinary flow rate between 6 and 15 mL/s (voided urine volume >150 mL). |
| Primary criteria of efficacy |
| I-PSS and QoL index were assessed at each month during the trial. |
| Peak flow rate was measured at each month during the trial. |
| The main comparisons were between measurements at month 6 and the baseline values. |
| Secondary criteria of efficacy |
| At baseline, and after 3 and 6 months: |
| Post-voiding residual volume. |
| Prostate volume. |
| Prostate-specific antigen. |

BPH, benign prostatic hyperplasia; I-PSS, International Prostate Symptom Score; QoL, quality of life.

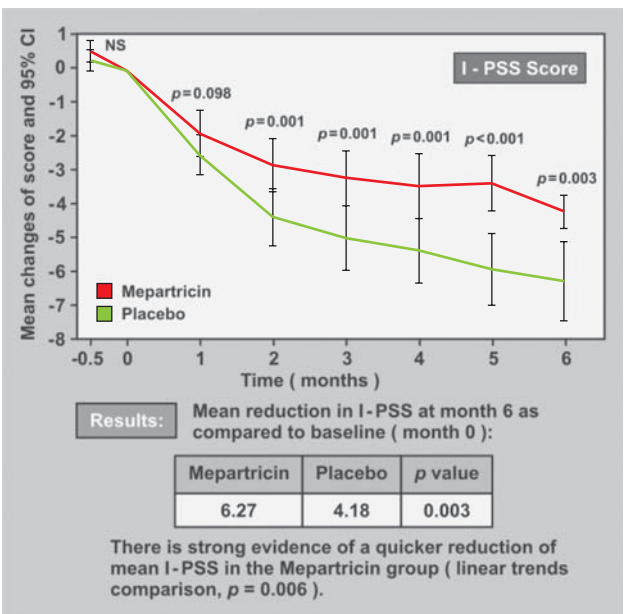


**Fig. 14** Influence of Mepartricin treatment on prostatic symptom score (I-PSS).

## Antiestrogen therapy with aromatase inhibitors

Aromatase inhibitors that inhibit the conversion of androstenedione and testosterone to estrone and estradiol-17β (Fig. 2), would logically

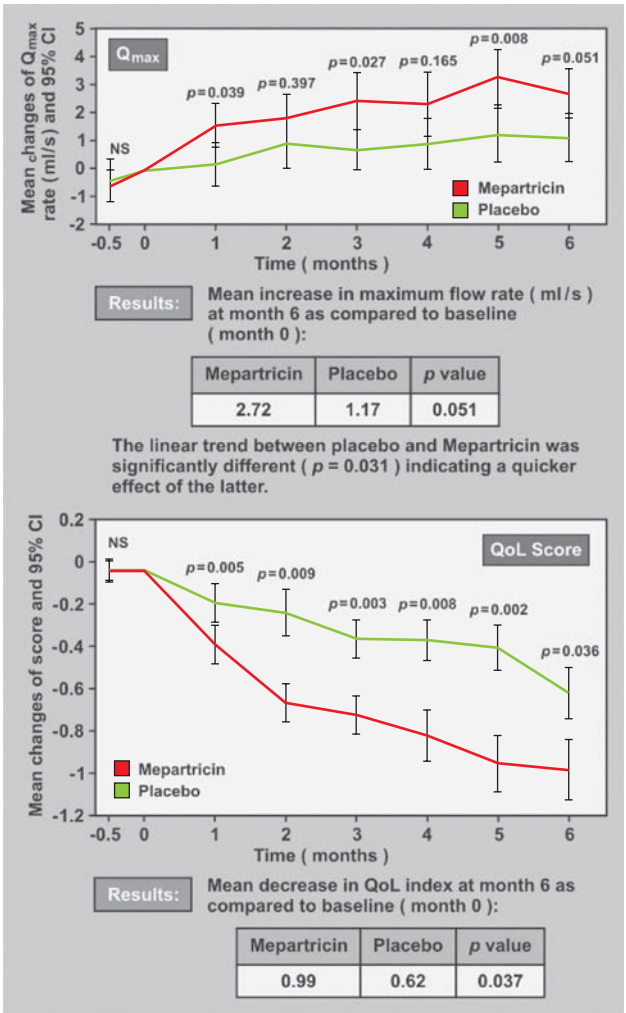


**Fig. 15** Influence of Mepartricin treatment on urine flow ($Q_{max}$) and on quality of life issues (QoL).

appear to offer another treatment option in the management of prostate disease. Nevertheless, the selective aromatase inhibitor, Atemestane was reported to have no effect on clinically established BPH,[132] a conclusion contrary to wide spread expectation and disappointing. Some believed that an effect on BPH resulting from decreased serum estrogens, was countered ineffectual, by the corresponding elevation in androgen levels.[133] Administration of an antiandrogen in association with an aromatase inhibitor offered another alternative, but interest waned, although Ito and colleagues have recently[134] described the effects of a new aromatase inhibitor, TZA-2237, that inhibited growth of both epithelial and stromal elements in hormone-induced canine BPH. A dual inhibition of estrogen and androgen levels, decreased smooth muscle growth and TZA-2237 was considered a potentially useful means of treating BPH.

## The broader acres: guidelines for prostate disease management

Estradiol-17β has assumed a position alongside the many and varied extrinsic and intrinsic factors that influence the growth and function of the prostate and this poses the question as to whether any form of 'antiestrogen therapy' should be included in options for treatment of BPH, cancer or prostatitis. Is there a role for Mepartricin and at which stage could a pure antiestrogen, or an aromatase inhibitor, be used for the management of prostate cancer. Although prostatitis and the associated inflammatory condition has long been an enigma, current attitudes encourage the need to understand better, the underlying molecular dysfunction behind this prostatic disorder. For those responsible for establishing clinical guidelines in support of disease management, recommendations that a diet which sustains from at least as early as adolescence, a high circulating level of genistein, does appear particularly onerous. The non-intrusive Mepartricin seems a reasonably logical 'antiestrogen' to consider for the management of BPH, possibly for men with early 'troublesome symptoms' recognized in their early 40s. Recommendations concerning the health value of high-fiber diets have long been universal. Could a combination of an 'antiestrogenic approach' in synergy with an antiandrogen be considered for the treatment of prostate cancer, an acceptable option for the high-risk patient after therapy for early cancer? Some might support such a combination for localized prostate cancer in a patient with a life expectancy of less than 5–10 years. The European guidelines for locally advanced prostate cancer indicate that if appropriate, watchful waiting can be considered if life expectancy is less than 5–10 years, the patient is asymptomatic and the Gleason score is between 4 and 5. Although hormone treatment is a valid option for other cases, the potential for 'antiestrogen' therapy could be considered in the light of the new research.

In the context of these comments, a recent review by Scherr and Reid Pitts,[135] that directed attention to the clinical rationale of androgen deprivation therapy without estrogen deprivation therapy for the management of prostate cancer, is noteworthy. They focus attention on the potential of the clinical efficacy of low daily 1 mg dose of DES, emphasizing its 'non-steroidal' effects. The 'therapeutic wheel' turns fully round, since the halcyon days of Huggins and Dodds, when the new synthetic estrogen was so enthusiastically hailed as the first orally active anticancer agent. Then, therapy passed through the troubled waters of Byar and the VA Cooperative Urological Research Group[136] and the reported cardiovascular problems associated with daily 5 mg DES. Nonetheless, a low daily dose of 1 mg. DES has generally been stated to be clinically effective[137,138] and many of the biologically beneficial effects of DES, reviewed by Scherr[135] and emphasized by others,[6] should be highlighted and re-assessed in relation to the differential signaling of the ER-isoforms and the influence of DES, not only on these growth regulatory networks, but on estradiol-17β mediated actions in the male. It is long accepted that non-steroidal antiestrogens and partial estrogens, acting like DES, inhibited prostate cancer growth.[139]

'Complete androgen blockade', that represses not only circulating testosterone, but also estradiol-17β levels,[140] is associated with increased bone resorption, osteoporosis, possible aberrant cognitive function, fatigue, hot flushes, as well as adverse cardiovascular problems. It must be remembered that estradiol-17β positively and negatively influences various aspects of vascular physiology, effects that can impact on blood flow, angiogenesis and cancer progression in the prostate gland. As stated earlier, complete repression of serum testosterone can provoke enhanced EGFR-mediated signaling, with ligand-independent AR-activation.[6] The conundrum surrounding the role of estrogens in relation to prostatic dysfunction is partially solved[141] and 'estrogens and the prostate' has grown up to become a reality and their regulatory potential for clinical management must now assume a therapeutic option over the coming years.

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