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# The Biology of Aging and the Development of Lower Urinary Tract Dysfunction and Disease

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## Introduction

Basic and translational research has played a critical role in the understanding of human structure and function and essentially all human diseases. This is certainly true of the aging process. Basic research has advanced our knowledge about anatomic and physiologic alterations that occur naturally as part of aging of the genitourinary tract. In addition, this type of research has led to the development of treatments for a wide spectrum of clinical conditions which predominantly affect older adults. This chapter will focus on basic and translation research related to prostate disease and bladder dysfunction in the elderly population. This includes analysis of benign prostatic

hyperplasia (BPH), prostatic fibrosis, and prostate cancer (PCa), and both storage and voiding dysfunction related to the bladder.

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## Prostate Disorders

### Prostatic Enlargement

#### Benign Prostatic Hyperplasia and Androgens

BPH is a noncancerous enlargement of the prostate and is a common condition associated with aging in men [1–3]. Normal prostate development is dependent on dihydrotestosterone (DHT), which is converted from testosterone by  $5\alpha$ -reductase enzymes. DHT is the major growth factor of adult prostate tissue [4]. In male rodents, castration results in prostatic involution due to massive apoptosis of the luminal epithelium and quiescence of the basal cell population. However, the prostate regenerates in castrate mice supplemented with DHT, showing that the adult prostate is highly sensitive and responsive to androgen [5–7]. Similarly, men who are castrated prior to puberty, have  $5\alpha$ -reductase-type 2 deficiencies, or have naturally occurring or clinically induced hypogonadism, do not develop a fully formed prostate and do not go on to develop BPH later in life [8].

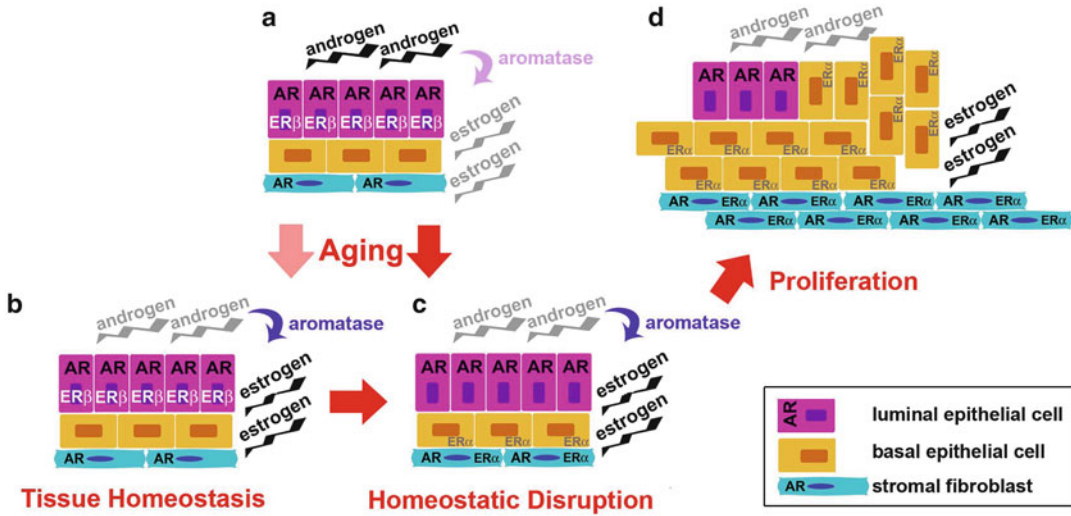
BPH comprises a gradual increase in prostatic volume that occurs over decades of life. Studies have estimated that BPH develops consequent to a low-level, but cumulative, cellular proliferation

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**Fig. 2.1** BPH and estrogens. (a) High androgen levels and ERβ expression levels in prostate epithelial luminal cells (pink) maintain luminal cell differentiation and quiescent basal epithelial (yellow) cell proliferation. (b) In the aging prostate, androgen levels decrease, aromatase activity increases, and androgens are increasingly converted to estradiols. These events can be countered by normal ERβ function, which helps maintain prostate luminal epithelial cells in a non- or low-proliferative, secretory state by facilitating estrogen-mediated antiproliferative and anti-inflammatory effects. This mechanism maintains tissue

and organ homeostasis under normal physiological conditions. (c) In the aging prostate, differential methylation of the ERβ and ERα promoters consequent to aging promotes estradiol-stimulated activation of ERα receptors in the basal prostate epithelium (yellow) and stromal fibroblast (blue) cells and consequent homeostatic disruption. (d) Increased expression and activation of ERα receptors in the aging prostate promotes both basal epithelial and stromal fibroblast cellular proliferation, facilitating BPH and prostatic enlargement

that increases post-pubertal prostatic volume by approximately 0.8–1.6 %, equivalent to only 0.2–0.4 mL, per year [9, 10]. Studies both in vivo and in vitro have reported higher proliferative and lower apoptotic rates for epithelial cells from hyperplastic compared to normal prostates, suggesting that some proportion of increased prostate volume with age is attributable to increased epithelial cell densities [11–13]. Work accomplished using rodent and rodent/human in vivo and in vitro models have suggested that paracrine interactions between glandular epithelial cells and adjacent fibroblastic stromal cells play an important role in the development of benign prostatic proliferative diseases [14–19]. These studies show that epithelial–stromal interactions are crucial for the regulation of epithelial cell growth and suggest that changes in such interactions consequent to aging likely contribute to the etiologies of BPH and PCa.

## BPH and Estrogens

Serum levels of both total and free testosterone decrease with age as documented in both the Massachusetts Male Aging Study [20] and the Baltimore Longitudinal Study of Aging [21]. Correlative findings show that intraprostatic and/or serum estrogen levels either do not change or are elevated consequent to aging in men [22, 23]. Recent studies have suggested that estrogenic hormones may promote prostatic enlargement in older men in a manner that largely correlates with the expression levels of the two primary estrogen cellular receptors, ERα and ERβ, which are expressed in different cellular compartments of the prostate gland. ERβ is primarily expressed by the prostate epithelium (Fig. 2.1a, b), whereas ERα is primarily expressed (often heterogeneously) by fibroblastic and epithelial prostate stromal cells (Fig. 2.1c). ERβ normally functions to help maintain prostate luminal epithelial cells

in a non- or low-proliferative, secretory state by facilitating estrogen-mediated antiproliferative and anti-inflammatory effects. This mechanism maintains tissue and organ homeostasis under normal physiological conditions. However, differential methylation of the ER $\beta$  and ER $\alpha$  promoters consequent to processes that are not entirely elucidated (but are likely related to aging) mediates decreased ER $\beta$  expression levels in prostate epithelium and increased ER $\alpha$  expression levels, particularly in the prostatic stroma. Thus, compared to normal prostate tissues, BPH tissues exhibit a high stromal ER $\beta$ /ER $\alpha$  ratio in association with stromal and epithelial hyperplasia (Fig. 2.1d) and tissue inflammation [8, 24, 25]. In addition, aromatase, the enzyme that converts testosterone to estradiol, is expressed and active in adipose tissue, adrenal glands, the testicles, and prostatic stroma, which suggests that local conversion of androgens to estrogens may promote estrogen signaling within the prostate [26, 27]. Aromatase expression and activity increase with the accumulation of obesity-related adipose tissue, resulting in reduced testosterone concentrations and concurrent increased estradiol production [28]. Obesity itself increases in incidence with age [29], suggesting that aging, obesity, increased aromatase expression and activity, and increased estradiol:testosterone ratios may play complex and intertwined roles in the development of prostatic enlargement and lower urinary tract symptoms (LUTS).

### BPH and Nonsteroidal Growth Factors

In addition to androgenic and estrogenic hormones, nonsteroidal growth factors have been identified that promote aging-associated prostatic enlargement. Most of these comprise small, soluble, secreted proteins, including basic fibroblast growth factor (bFGF, FGF-2) [30], insulin growth factors (IGFs) [31], and inflammatory molecules [32, 33].

#### bFGFs

bFGFs and their receptors are highly expressed in BPH tissues [34, 35], primarily in stromal fibroblasts, smooth muscle, and endothelial cells [36], and promote the proliferation of stromal fibroblasts

in vitro [30]. bFGF is also highly expressed by adipose tissues [37], suggesting another avenue through which obesity may promote prostatic enlargement. In vivo studies have shown that targeted transgenic expression of bFGF in the mouse prostate exhibit epithelial hyperplasia and glandular enlargement [38]. Taken together, these studies consistently demonstrate one or more role(s) for bFGF in prostatic enlargement.

#### IGFs

IGF receptors are expressed in the epithelium [39] and stroma [40] of BPH tissues at elevated levels compared to normal prostate. Expression of the IGF-II gene is biallelic in histologically normal tissues and adjacent malignant glands, but demonstrates an imprinted, paternally imprinted allelic expression in BPH tissues [41]. Mice engineered to overexpress IGF-1 in the mouse prostate exhibit denser, enlarged glands compared to non-transgenic littermates [42]. Interestingly, IGF-1 levels are upregulated by estradiol binding to the ER $\alpha$  receptor [43], suggesting a mechanism whereby increased aromatase activity in the aging prostate (especially in obese individuals) may promote IGF-1 expression and activity.

#### Inflammatory Molecules

Inflammatory molecules secreted in association with aging tissues that may promote prostatic enlargement include the interleukins and chemokines. The interleukins comprise a large family of related proteins that function to control innate immune responses and as cytokines (growth factors) for many cell types [44]. The primordial interleukins, Interleukin-1 $\alpha$  (IL-1 $\alpha$ ) and Interleukin-1 $\beta$  (IL-1 $\beta$ ), accomplish multiple functions in multiple cell types. Of importance to this discussion is that IL-1 $\alpha$  and IL-1 $\beta$  activate the powerful NF $\kappa$ B transcription factor which, in turn, promotes the transcription of scores of genes encoding inflammatory proteins, including TNF $\alpha$ , CC-type chemokines, CXC-type chemokines, and interleukins (including IL-1 $\alpha$  and IL-1 $\beta$ ) [45]. Many of these same inflammatory proteins (especially IL-6 and TNF $\alpha$ ) are elevated in older adults, often in conjunction with increased obesity and adiposity and with decreased testosterone in men [46].

A recent study found that stromal fibroblast cells cultured from the prostates of older men (aged 63–81 at the time of prostatectomy) were less able to suppress the proliferation of nonmalignant prostate epithelial cells than those cultured from the prostates of younger men (aged 40–52 years) [47]. Moreover, these studies showed that the transcriptome of aging prostate stroma is characterized by the upregulation of several genes that encode secreted inflammatory mediators, including CXC-type chemokines (CXCL1, CXCL2, CXCL5, CXCL6, CXCL12), interleukins (IL11, IL33), and transcripts with cytokine homology (CYTL1) [47, 48].

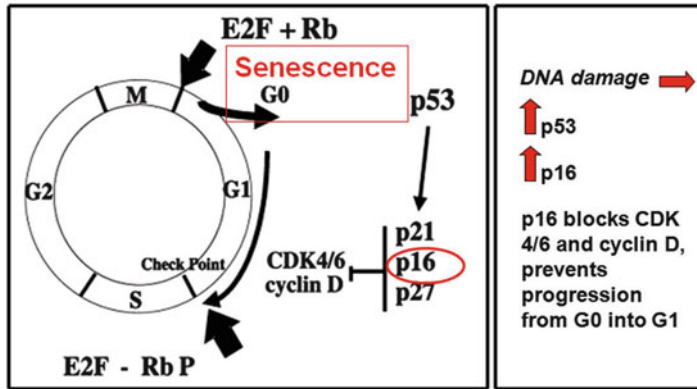
Fibroblastic cells cultured from the prostates of older men secreted higher levels of CXCL1, CXCL5, CXCL6, and CXCL12 protein than those cultured from the prostates of younger men [47, 48]. Subsequent studies have confirmed the secretion of CXCL5, CXCL12 [49], CXCL8 [49, 50], CXCL10, and IL-6 [50] by human prostate stromal fibroblastic cells. Fujita et al. [51] demonstrated >2-fold higher levels of IL-1 $\beta$ , IL-7, CCL2, and IL-6 in the extraprostatic secretions (EPS) of large (>60 g) compared to small (<40 g) prostates and showed that the source of CCL2 secretion was prostate stromal fibroblastic (but not epithelial) cells. High levels of CCL2 secretion by prostate stromal fibroblast cells was also demonstrated by McDowell et al. [49]. Together, these studies suggest that a diverse and robust chemokine “secretome” is expressed by stromal fibroblast cells in the human aging and enlarged prostate.

### **Mechanisms that Promote the Secretion of Nonsteroidal Growth Factors in the Aging Prostate**

With the exception of those cell types that comprise continually renewing tissues originating from particular types of stem cells, many types of mammalian cells become growth-arrested, or senescent, over time. By definition, senescent cells are nonreplicative. Cells may become senescent because they have reached their Hayflick limit, i.e., their chromosomal telomeres are too short to permit further DNA synthesis

and cell division. Such cells have effectively reached replicative exhaustion and have entered replicative senescence. Cells may also become senescent because they have become stressed, often resulting in DNA damage and growth arrest. Although these cells have not reached their Hayflick limit, they are, nevertheless, nonreplicative and have entered cellular senescence. Many studies have shown that senescent cells accumulate with age in vivo [52–56]. Senescence is essentially controlled by tumor suppressor genes, including p16, Arf, p53, and RB1, that serve as checkpoints to prevent the proliferation of cells at risk for neoplastic transformation [57, 58] (Fig. 2.2).

Prostatic stromal fibroblasts induced to undergo senescence after achieving replicative exhaustion or after exposure to agents that caused oxidative stress or DNA damage demonstrate similar and significant upregulation of transcripts encoding several inflammatory mediator-type proteins, including the chemokines CXCL1, CXCL8, CXCL12, CCL2, CCL7, CCL11, CCL13, and CCL20 [59]. Fibroblasts induced to undergo replicative exhaustion or irradiation-induced senescence secreted diverse inflammatory mediator proteins, including the interleukins IL-1 $\beta$ , IL-6, IL-7, IL-11, IL-13, and IL-15; the CC-type chemokines CCL2, CCL3, CCL8, CCL13, CCL16, CCL20, and CCL26; and the CXC-type chemokines CXCL1, CXCL2, CXCL3, and CXCL8 [60]. Thus, fibroblastic cells derived from multiple organs, including the prostate, demonstrate senescence-associated secretory profiles (SASPs) that are remarkably similar to each other and to those isolated from aging and/or enlarged human prostates [47, 48, 50, 51]. Moreover, normal human prostate epithelial cells induced to undergo senescence subsequent to ionizing radiation demonstrated a senescence-associated secretome that was very similar to that exhibited by senescent fibroblasts [60]. Taken together, these studies are consistent with the accumulation of senescent stromal fibroblasts as a potential driving force behind inflammatory protein secretion in the aging and enlarged human prostate.



**Fig. 2.2** Senescence and the cell cycle. Low-level DNA damage states in the cell include terminal telomere shortening at cellular replicative exhaustion or those produced by exposure to various stresses (oxidative stress, chemical insult, inflammation). Consequently,

p53 and p16 protein levels increase, and high p16 levels block progression of the affected cells at G0 in the cell cycle. The cells effectively exit the cell cycle and enter a proliferatively quiescent (but metabolically very active) state of senescence

### Mechanisms Through Which Inflammatory Proteins Promote Prostate Cell Proliferation

BPH/LUTS is pathologically characterized by the proliferation of fibroblast/myofibroblast and epithelial cell types within the periurethral, or transitional zone, region of the prostate gland [1, 2, 61]. Previous studies have shown that BPH/LUTS develops consequent to a gradual increase in prostatic volume that occurs over decades of life through a process of low-level, but cumulative, cellular proliferation that increases post-pubertal prostatic volume by approximately 0.8–1.6 %, equivalent to only 0.2–0.4 mL, per year [9, 10]. Therefore, the observed low-level secretion of multiple chemokines by prostatic stroma and resident inflammatory cells may promote the concomitant low-level, but cumulative, overproliferation of both stromal fibroblastic and epithelial cell types associated with increased prostate volume in aging men.

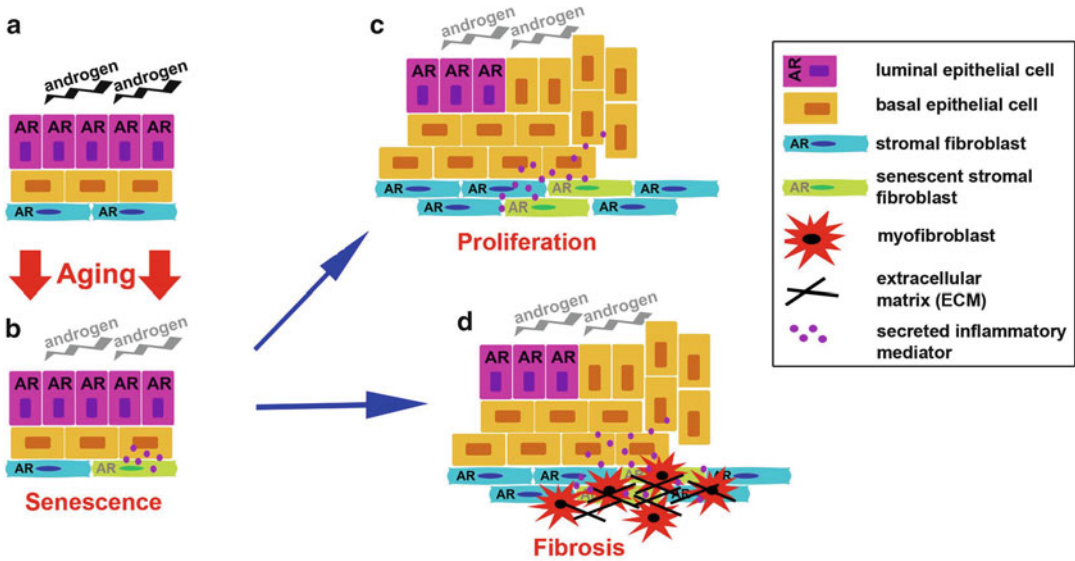
In vitro studies have shown that nonmalignant prostate epithelial cells respond proliferatively when cocultured with senescent prostate stromal fibroblasts in vitro [59]. Many of the CC- and CXC-type chemokines identified as secreted by senescent cells have been shown to induce proliferative responses in vitro [47–49, 51, 59, 62] (Fig. 2.3b, c). Transgenic mice engineered to over-

express keratinocyte-derived chemokine (KC), the functional murine homolog of CXCL8, exhibit hyperplastic prostatic epithelium, characterized by age-associated acinar infolding and significant increases in acinar diameter in vivo [63]. Moreover, many of these same CC- and CXC-type chemokines are highly angiogenic and promote tissue vascularization [64]. A small number of studies have demonstrated increased microvessel density (MVD) in BPH/LUTS compared to normal prostate tissue [65] and even in BPH/LUTS compared to malignant tissue [66]. These studies provide some rationale for exploring chemokine-mediated angiogenesis as a contributing factor to BPH/LUTS development and progression.

### Prostatic Fibrosis

Fibrosis is an aberrant version of the normal wound healing process and is characterized by myofibroblast accumulation, collagen deposition and extracellular matrix (ECM) remodeling, and increased tissue stiffness [67–70]. Numerous studies have demonstrated that aging- and inflammation-associated fibrotic changes in tissue architecture contribute to dysfunction and disease in multiple organ systems. Examples include pancreatic dysfunction in type 2 diabetes [71, 72],





**Fig. 2.3** Senescence can promote cellular proliferation and tissue fibrosis. (a) High levels of androgen help maintain tissue homeostasis in the prostate. (b) Aging-associated replicative exhaustion, exposure to various stresses, and declines in androgen levels induce the senescence of some stromal fibroblasts (green) in the prostate. Senescent stromal fibroblasts are secretory cells and produce high levels of inflammatory mediators (purple dots). (c) Inflammatory mediators secreted by senescent cells may act as cytokines to promote the proliferation of epithelial (yellow) as well as fibroblast (blue) cells, promoting

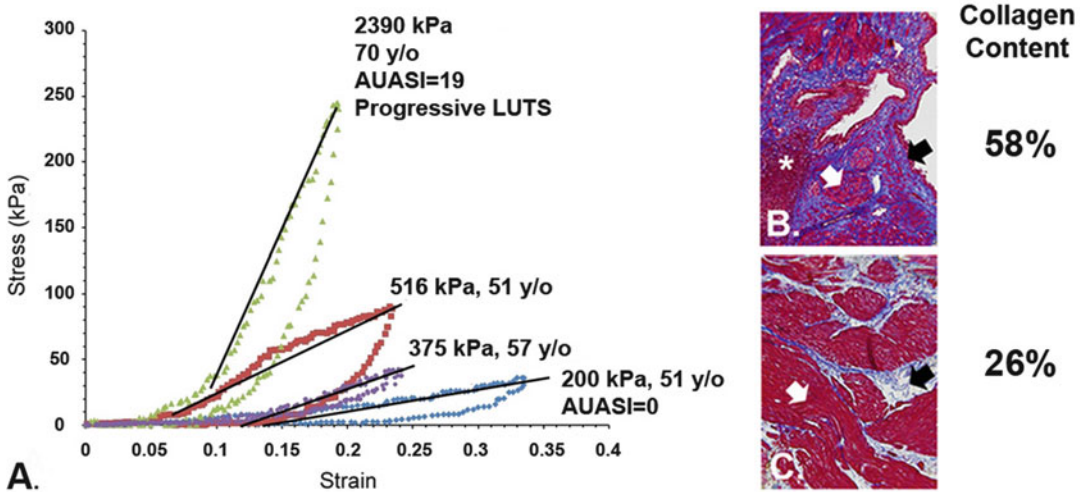
prostatic enlargement. (d) Inflammatory mediators (purple dots) secreted by senescent cells (green) may also promote resident fibroblast (blue) or other (fibrocytes, pericytes) cell types to undergo myofibroblast differentiation (red stars). Myofibroblasts accumulate and secrete extracellular matrix (ECM) components such as fibronectin and collagen (black fibers). If these changes occur in periurethral tissues, the subsequent increased stiffness may reduce urethral compliance and thereby contribute to obstructive symptoms

chronic obstructive pulmonary diseases [73, 74], cirrhotic nonalcoholic fatty acid liver disease [75, 76], Crohn's Disease, and parts of the spectrum disorder termed inflammatory bowel disease (IBS) [77, 78].

Myofibroblast accumulation and differentiation contributing to tissue fibrosis occurs through a sequence of events initiated by activated TGF- $\beta$  (primarily TGF- $\beta$ 1; subsequent references to TGF- $\beta$  are to TGF- $\beta$ 1). Activated TGF- $\beta$ 1 binds to the transmembrane TGF- $\beta$ RII receptor, which then simultaneously heterodimerizes with and phosphorylates the TGF- $\beta$ RI receptor, which, in turn, phosphorylates Smad2 or Smad3. Activated Smad2 or Smad3 then translocate as Smad2/Smad3 or Smad3/Smad4 complexes into the nucleus to promote gene transcription. Initial events in myofibroblast differentiation include Smad-mediated expression of the alpha-smooth

muscle actin ( $\alpha$ SMA) and collagen I (COL1) genes [68, 70].

Myofibroblast accumulation and differentiation have been observed in the prostates of mouse models of BPH/LUTS. Targeted expression of a constitutively active TGF- $\beta$ 1 to the murine prostate gland epithelium promotes fibroplasia and the development of collagenous micronodules in collapsed acini, phenotypes consistent with myofibroblast accumulation, and tissue fibrosis [79]. Similarly, transgenic mice engineered to overexpress keratinocyte-derived chemokine (KC), the functional murine homolog of CXCL8, exhibit hyperplastic prostatic epithelium, characterized by age-associated acinar infolding and significant increases in acinar diameter. Moreover, overexpression of KC was associated with a prototypical reactive stromal phenotype characterized by myofibroblast accumulation [63].



**Fig. 2.4** Evaluation of periurethral prostate tissue stiffness and collagen content. (a) Stress/strain curves of periurethral prostate tissues from four patients. A high tangent modulus of 2,390 kilopascals (kPa) was obtained for tissue from a 70 year old man with progressive LUTS and self-reporting an American Urological Association Symptom Index (AUASI) score of 19, whereas a low tangent modulus of 200 kPa was obtained for tissue from a 51 year old man self-reporting an AUASI score of 0. (b) Masson's Trichrome stained section of tissue tested

from the 70 year old man reporting an AUASI score of 19 in (a) demonstrates dense collagen fibrils (blue) and a total collagen content of 58 %. (c) Masson's Trichrome stained section of tissue tested from the 51 year old man in a. reporting an AUASI of 0 demonstrates few collagen fibrils (blue) and a total collagen content of 26 % (Reprinted from Ma J, Gharaee-Kermani M, Kunju L, Hollingsworth J, Adler J, Arruda E, et al. *Prostatic Fibrosis is Associated with Lower Urinary Tract Symptoms. The Journal of Urology.* 2012)

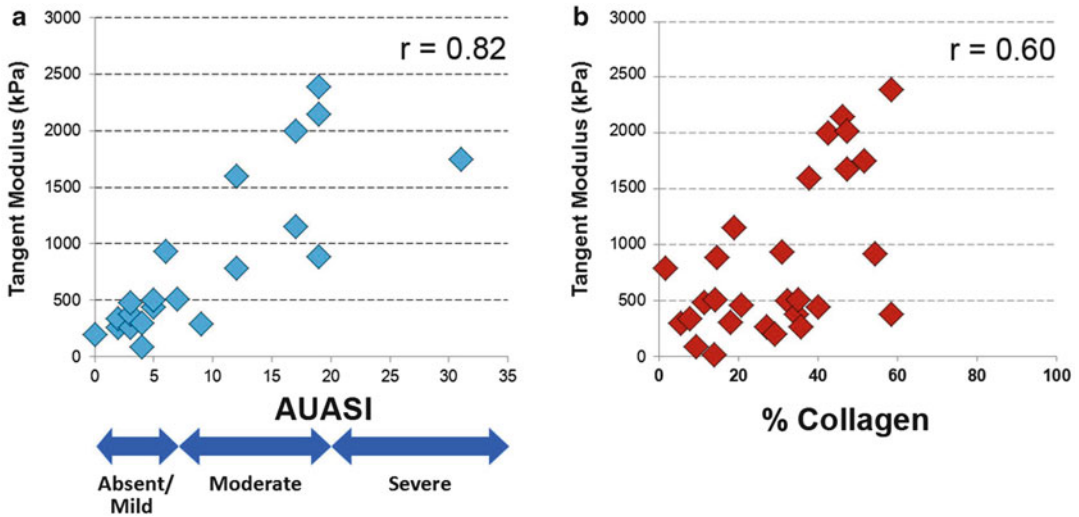
In the human prostate, myofibroblast accumulation and tissue fibrosis were recently shown to be associated with LUTS. Periurethral prostate tissues from men with self-reported high American Urological Association Symptom Index (AUASI) scores in the moderate-severe range were mechanically stiffer and exhibited significantly higher collagen content compared to men with lower AUASI scores in the absent/mild range (Fig. 2.4). Among tissues from 21 patients, measures of tissue stiffness for 9 with AUASI scores in the moderate/severe range were significantly higher than for those tissues from the 12 patients with scores in the absent/mild range ( $r=0.82$ ). This indicates that higher levels of tissue stiffness are directly correlated with moderate/severe LUTS (Fig. 2.5a) and also with higher levels of collagen content ( $r=0.60$ ) (Fig. 2.5b). This study clearly demonstrated direct associations between high levels of tissue stiffness, with increased collagen content and fibrosis, and the further association of all of these measures with

LUTS [80]. Increased periurethral tissue stiffness consequent to aging likely reduces urethral compliance and thereby contributes to obstructive symptoms.

## Prostate Cancer

### Prostate Cancer Epidemiology

Prostate cancer is a significant public health issue in the USA. Prostate cancer is the leading cause of newly diagnosed cancers, the second leading cause of cancer-related deaths in American men [81], and is the most commonly diagnosed non-skin cancer. The American Cancer Society estimates that in 2011, approximately 240,890 men were diagnosed with prostate cancer and 33,720 men died of the disease. In Europe, there are about 80,000 deaths a year from PCa, whereas in the USA 27,050 deaths and 218,890 new cases were reported in 2007 (<http://www.cancer.gov>).



**Fig. 2.5** AUASI scores correlate with tissue stiffness and collagen content. **(a)** Among tissues from 21 patient tests, measures of tissue stiffness for 9 with AUASI scores in the moderate/severe range were significantly higher than for those tissues from the 12 patients with scores in the absent/mild range ( $r=0.82$ ), indicating that higher levels

of tissue stiffness directly correlated with moderate/severe LUTS. **(b)** Higher levels of tissue stiffness directly correlated with higher levels of collagen content ( $r=0.60$ ). These data show that high levels of tissue stiffness correlate with collagen content and fibrosis, and further correlate with LUTS

### PCa and Aging

Older age, African American race, and a family history of the disease can all increase the likelihood of a man being diagnosed with prostate cancer. PCa is strongly age dependent. As men increase in age, their risk of developing prostate cancer increases exponentially. Although only 1 in 10,000 under age 40 will be diagnosed, the rate shoots up to 1 in 39 for ages 40–59, and 1 in 14 for ages 60–69. More than 65 % of all prostate cancers are diagnosed in men over the age of 65 (<http://www.pcf.org>). The relationship between PCa incidence and aging is consistent across ethnic and racial groups.

### Androgen/Androgen Receptor (AR) Signaling and Aging

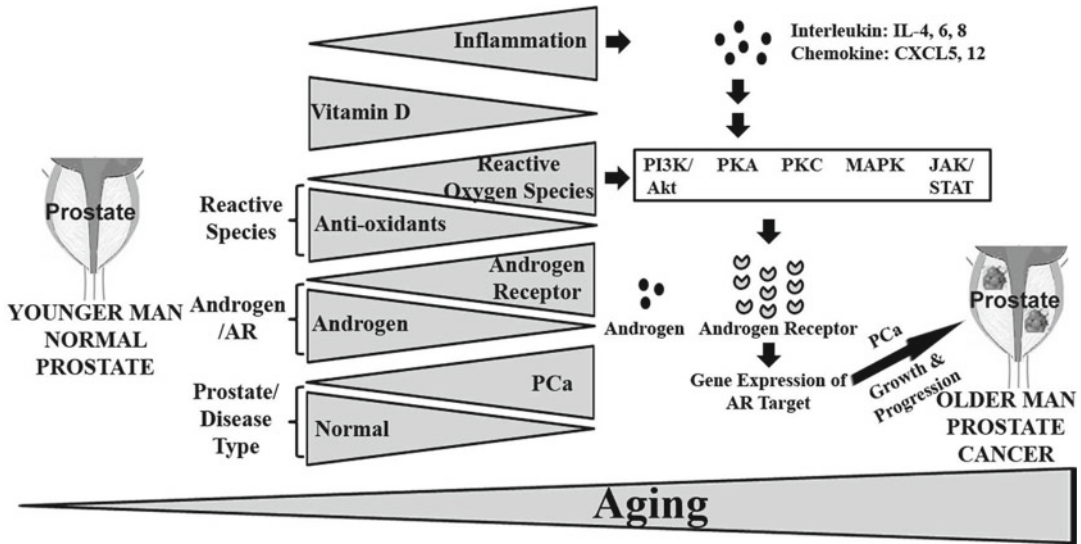
Prostate tumors are initially dependent on androgen signaling and can be successfully controlled by a series of strategies that deplete endogenous androgen expression or interfere with AR-mediated signaling. However, several studies document a progressive decline in the production and tissue levels of the major androgen, testosterone, with age. In contrast, the AR itself is upregulated with

age in men and promotes continued proliferation and differentiation of the prostate [82, 83]. Therefore, therapeutic approaches that directly target androgen and/or the AR are only effective for early stage androgen-dependent prostate cancer, as progressive prostate tumors develop alternative strategies to survive and grow despite anti-androgen therapy. Eventually, such tumors develop into lethal, metastatic castration resistant prostate cancers [84] (Fig. 2.6).

### Nonsteroidal Growth Factor/AR Signaling and Aging

Despite reduced levels of androgen with aging, the AR is constitutively active and plays an important role in progressive castration resistant disease. Several studies have reported hormone-independent AR signaling in prostate cancer cells by nonsteroidal growth factors such as peptide growth factors [85–90]; neuropeptides, including neurotensin and bombesin [91–94]; inflammatory mediators such as interleukins IL-4 and IL-6 [95–107]; and chemokines CXCL8 [108–111] and CXCL12 [112] (Fig. 2.6). Several of these nonsteroidal growth factors are secreted in excess





**Fig. 2.6** Aging promotes prostate cancer progression. Aging-associated decline in the androgen levels is accompanied by an increase in androgen receptor (AR), reactive oxygen species (ROS) and inflammation, and a decrease in antioxidants and vitamin D. Inflammatory molecules (Interleukins and chemokines) secreted by aged prostate

activates different signal transduction pathways, also activated by an increased reactive species (ROS), which then activates the androgen receptor (AR). Activated AR drives the expression of AR target genes and thus promotes the prostate cancer growth and progression

by the aging prostate and promote prostate cancer. As noted earlier in this chapter, CXCL5 and CXCL12 are secreted at high levels by aging prostate stroma [47, 113], and both CXCL5 and CXCL12 have been shown to promote prostate cancer progression [113–115]. Another study has also found that the serum levels of CXCL8 are elevated in aged men with prostate cancer and bone metastasis [116]. These nonsteroidal growth factors activate different signal transduction pathways like PI3K/Akt, MAPK, PKC, PKA, and JAK/STAT (Table 2.1) [93–96, 99, 101, 104–106, 108–110, 112, 117–120], which further activates the AR, drives AR target genes, and promotes PCa growth and progression (Fig. 2.6).

### Oxidative Stress and Aging

Aging is also characterized by an increase in intracellular oxidative stress and a decrease in intracellular reactive oxygen species (ROS) scavenging. The increased oxidative stress with aging activates various signal transduction pathways like PI3K/Akt, MAPK, PKA, PKC, and JAK/STAT which activates AR signaling and thus PCa

growth and progression (Table 2.1). In addition, increased oxidative damage to cellular macromolecules in the prostate has been observed in aging [121] as well as during the development of prostatic malignancy [122, 123]. Specifically, the increase in oxidative damage to DNA, measured by the accumulation of nuclear 8-hydroxydeoxyguanosine (8-OHdG), has been observed in aging prostate tissues [124]. Glutathione (GSH) is the most abundant antioxidant in cells and tissues, and it plays a primary role in protection against oxidative stress [125]. Depletion of GSH with aging is responsible for increased risk for cancer in older adults [126]. Like glutathione, selenium blood levels decrease with age [127–129]. Selenium is protective against prostate cancer through the reduction of oxidative stress compounds [130, 131]. Clinical chemoprevention trials support the protective role of selenium against cancer development including prostate cancer [132, 133]. A role for oxidative stress in prostate cancer is supported by observations that foods high in antioxidants such as fruits and vegetables are protective [134],

**Table 2.1** Non-steroidal growth factors and inflammatory proteins mediate androgen receptor activation in prostate cancer cells

Inflammatory protein	Signal transducing proteins	References
IL-4	Akt, NFkB, p300	[101, 104, 106]
IL-6	STAT3, SRC-1, p300, PI3K/AKT, STAT3, MAPK	[93–96, 99, 105, 117, 120]
CXCL8 (IL-8)	EGFR, Src, Akt, NFkB, ERK, PI3K/Akt, Src	[108–110, 119]
CXCL12 (SDF-1)	SRC-1, MAPK, PI3K/Akt	[112]

and also by clinical studies which indicate that intake of antioxidants, such as selenium,  $\alpha$ -tocopherol (vitamin E), and the carotenoid lycopene offers protection against prostate cancer.

### Vitamin D and Aging

Vitamin D insufficiency and deficiency are highly prevalent among adult men in the USA [135]. Vitamin D deficiency is associated both with moderate-severe LUTS [135] and with an increase in risk for prostate cancer [136]. Low serum levels of 1,25-D, a vitamin D metabolite, were significantly associated with an increased risk of clinically detected prostate cancer among older men, particularly in men with low levels of 25-dihydroxyvitamin D (25-D) [137]. Therefore, high dose vitamin D alone or in combination with other agents has been shown to be effective in prevention of prostate cancer [138].

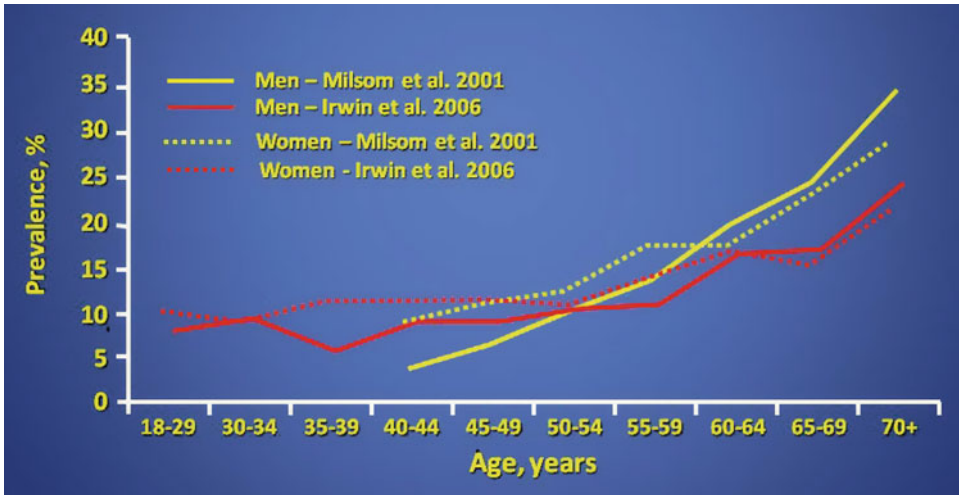
### Prostate Summary

Aging-associated changes in prostate tissues are promoted by complex biological processes. Transitions in the expression levels and activities of steroidal hormones and nonsteroidal growth factors during the aging process disrupt tissue homeostasis within the prostate and facilitate cellular proliferation, organ enlargement, and malignant growth. The observed low-level secretion of inflammatory proteins within aging prostate tissues promotes the concomitant low-level, but cumulative, overproliferation of both

stromal fibroblastic and epithelial cell types. This is associated with increased prostatic volume in aging men and may promote hormone-independent growth of prostate tumors. Many of these same proteins promote other cellular processes in the prostate, including myofibroblast accumulation and tissue fibrosis. This can also contribute to the development and persistence of LUTS in aging men. Though far from complete, a picture is beginning to emerge for how the biology of aging promotes changes in prostatic tissue that contribute to LUTS and malignant growth. These findings may point the way toward development of diagnostic and prognostic tools as well as preventive and therapeutic approaches that will be useful for the detection and treatment of male LUTS and PCa.

### Bladder Dysfunction

The prevalence of overactive bladder (OAB) and other LUTS increases with age and has a considerable negative impact on quality of life. The International Continence Society (ICS) has defined OAB as a symptom complex with urinary urgency, with or without urinary incontinence, and nocturia [139]. Detrusor overactivity (DO) is a urodynamic diagnosis associated with demonstration of involuntary bladder contractions during cystometry. Many studies have described the epidemiology and age-dependency of LUTS (Fig. 2.7). The EpiLUTS study surveyed a total of 30,000 women and men in the USA, UK, and Sweden between the age of 40 and 95 years of age, using an Internet-based self-administered data collection. LUTS were found to be highly prevalent in this population study and increased with advancing age in men. Increasing age in women was associated with a higher prevalence of only certain LUTS, such as urgency, urgency with fear of leaking, weak stream, urgency incontinence, and nocturnal enuresis [140]. The National Overactive Bladder Evaluation (NOBLE) specifically assessed the prevalence of overactive bladder (OAB) symptoms in a US adult population over 18 years of age. The prevalence of OAB symptoms was 16.9 % in women and 16.0 % in men and



**Fig. 2.7** Prevalence of OAB by age. Data from Milsom et al. *BJU Int.* 2001;87:760–766 and Irwin et al. *Eur Urol.* 2006 Dec;50(6):1306–14

showed a steep increase with age in women when associated with urgency incontinence. A similar pattern was observed for OAB in men without urgency incontinence, with a threefold increase in individuals more than 55 years of age as compared to those younger than 45 years [141]. OAB symptom prevalence increased with age in both men and women in the EpiLUTS study as well [142]. Wehrberger et al. [143] studied the prevalence of LUTS and UI in a population-based cohort analysis of men and women over 85 years of age in the Vienna Trans-Danube Aging Study (VITA). OAB was reported as 55 % in women and 50 % in men, and UI was found in 35 % of women and 24 % of men. Essentially all epidemiological studies are in accordance and demonstrate that LUTS and overall voiding dysfunction increase with age in both men and women. The proportion of individuals aged 80 years or older is currently the fastest growing sector of the population worldwide [144], and this implies that analysis of age-dependent factors contributing to bladder dysfunction will be urgently needed to develop strategies for managing the problem.

Physiological aging affects lower urinary tract function at all levels of the organism, from changes in the central (CNS) and peripheral (PNS) nervous systems to biochemical and cellular alterations within the detrusor and urothe-

lium of the bladder and urethra. These changes and their functional consequences are briefly discussed in this overview.

### Age-Related CNS Changes in Adults with Urinary Incontinence

Normal aging may affect neurons in the CNS at a cellular and synaptic level. Just as cognitive decline has been observed in older humans without associated neurodegenerative disease, the age-associated myelin or neuronal loss can lead to impaired inhibitory control of micturition. Control of micturition involves several regions of the brain coordinating afferent and efferent signaling of the storage and micturition reflexes [145]. Common changes in cortical pathways seen in older adults could involve the regions of the brain responsible for voiding control. Griffiths et al. [146] used functional magnetic resonance imaging (fMRI) in 10 continent women aged 30–79 years to study regional brain responses during bladder filling via urethral catheter. Activation of bilateral insula and dorsal anterior cingulate cortex decreased with age. The authors interpreted their results to suggest that with increasing age, weaker signals in the bladder control network as a whole and/or changes in

medial prefrontal cortex function, which exerts inhibitory control of the pontine micturition center (PMC), or connecting pathways may be responsible for the development of urgency incontinence.

White matter changes were associated with urinary complaints in a cohort of nondisabled elderly people in the Leukoaraiosis And DISability (LADIS) Study [147]. White matter hyperintensities (WMH) seen on MRI in the right inferior frontal region correlated with incontinence, incontinence severity, and degree of bother in a cohort of 100 community-dwelling individuals [148]. In another study, Tadic et al. [149] demonstrated by fMRI that brain activity in 25 women with UI during bladder filling was positively correlated with global WMH in the PMC. Their findings provide some clues to the possible role of white matter damage in the genesis of urgency incontinence and to the cerebral mechanisms of bladder control in older women.

### **PNS Alterations Can Occur with Age-Related LUTS**

Parasympathetic and sympathetic preganglionic neurons project to the major pelvic ganglion to make contact with postganglionic neurons innervating the bladder and urethra. Age-related changes in innervation leading to micturition disturbances have been extensively studied in animals and humans. In humans, Gilpin et al. [150] determined the effect of age on the autonomic innervation of the urinary bladder in a group of 54 patients with an age range of 20–79 years, all of whom had a normal urodynamic study. They reported a reduction in the number of nerves with progressing age, as did Hald and Horn [151]. In aged rats, voiding dysfunction was attributed to a loss of monoaminergic innervation of the lumbosacral spinal nuclei [152]. They found by quantitative image analysis significant age-associated declines in the innervation of most regions, including the intermediolateral cell nucleus, sacral parasympathetic nucleus, dorsal gray commissure, and in the ventral horn, including the dorsolateral nucleus, which in the rat is one of the component

nuclei homologous to Onuf's nucleus in humans. Lesions in Onuf's nucleus are associated with voiding dysfunction characteristic of Shy-Drager syndrome. Mohammed and Santer [153] found that the total neuronal numbers of rat lumbosacral primary afferent neurons did not change with age (from 3 to 24 months of age). However, the effects of NO on the bladder and also its expression in dorsal root ganglion neurons were reduced in aged rats [139, 154]. Similarly, a reduction in vanilloid receptor type 1 in the lumbosacral dorsal root ganglia was found in older rats [155]. In anesthetized rats, Hotta et al. [156] showed that compared to young adult animals (2–3 months), aged rats (26–29 months) exhibited (1) bladders with nearly six times higher volumes; these volumes were accommodated at lower pressures; (2) reduction of bladder contractions induced by pelvic nerve stimulation; and (3) a decrease of the pelvic afferent nerve activity sensing bladder volume. They attributed their findings to (a) changes in the mechanical properties of the bladder, (b) changes in the contractile properties of the detrusor smooth muscle during efferent stimulation, and (c) changes in the ability of its afferent innervation to sense bladder volume. They also suggested that such changes could explain the increase in residual volume, the inability to postpone voiding, and the decrease in flow rate seen in elderly humans.

The conduction velocity of myelinated and unmyelinated fibers of the pelvic nerve in rats was found not to change with age. Only the number of unmyelinated fibers was significantly reduced in older rats, particularly those with a diameter smaller than 0.7  $\mu\text{m}$  [157]. Further evidence for an age-dependent reduction in sensory functions was presented by Smith et al. [158], who suggested that their calculations approximating wall stress during filling indicated loss of bladder volume sensitivity with increasing age. The findings by Kenton et al. [159] support age-dependent reduction of sensory functions also in humans. They compared current perception thresholds (CPT) in the urethra and bladder of women with idiopathic overactive bladder to asymptomatic controls and demonstrated that the CPT was significantly higher in older women.

This suggests that sensory neuropathy in the lower urinary tract increases with age and may contribute to the increase in OAB/DO seen with aging.

### **Age-Related Bladder Remodeling: Structural Changes of the Bladder and Urethra**

A morphometric study of human bladder specimens from two different age groups revealed that the area density of smooth muscle to connective tissue ratio decreased with age in both men and women [160], suggesting that aging is associated with a relative increase in detrusor fibrosis. This is not in agreement with some reported findings in rats, where morphometric analysis showed a significant age-dependent increase in the mean thickness of the muscularis layer, whereas the collagen density significantly decreased in the muscularis and in the lamina propria layers [161]. However, in another study, histological examination of the bladder of older Fisher rats revealed urothelial thinning, decreased muscle mass, and increased collagen content [162]. Thus, reports on the effects of aging on rat bladder morphology show conflicting results, suggesting that the aging process in animals may not reliably reflect what is occurring in humans.

A reduced number of caveolae (invaginations of the plasma membrane) in bladder smooth muscle cells have been observed in human [163] and rat specimens [164]. Since the caveolae provide a mechanism for compartmentalization and integration of signal transduction, they play an important role in normal smooth muscle function. However, their precise role in age-related detrusor dysfunction remains to be established.

Levy and Wight [165] observed a significant increase of collagen fibers in the lamina propria and around the neurovascular bundles of human bladders, and Ewalt et al. [166] noticed a replacement of elastin by collagen within the muscle fibers accompanied by increased collagen deposits at the basal membrane. These findings were suggested to explain the reduced elasticity and potentially the reduced bladder capacity of the aging detrusor. Strasser et al. [167] found that age

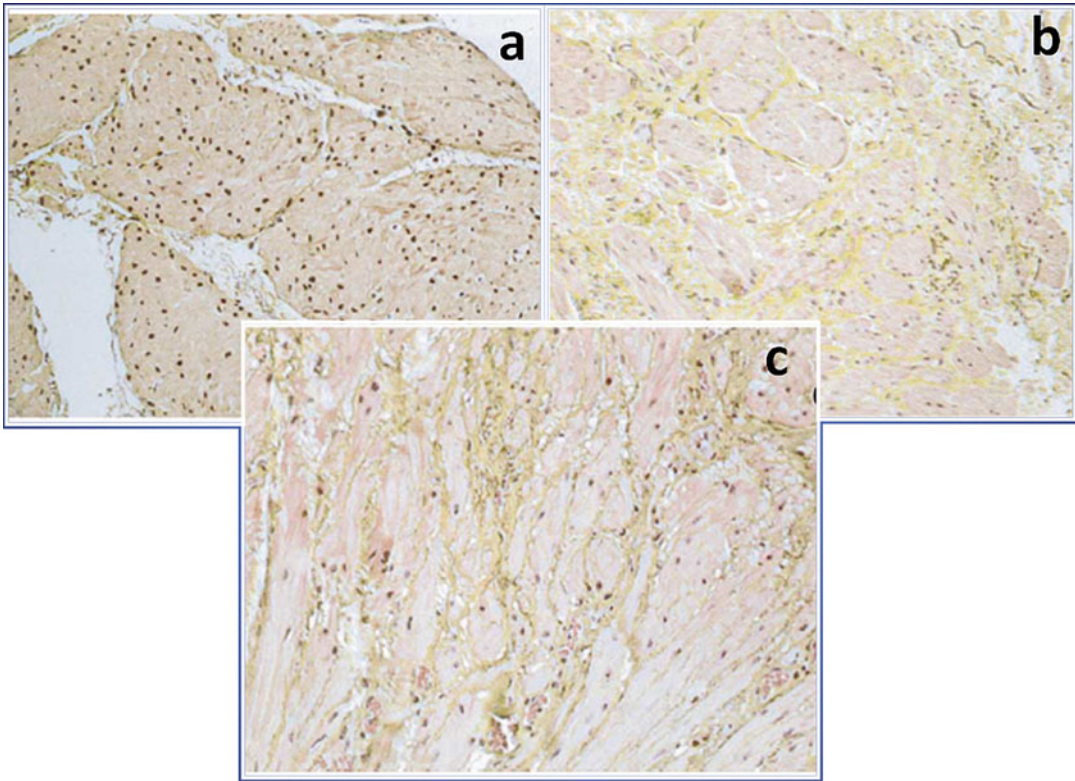
was associated with apoptosis of striated muscle cells in a cadaver study of the rhabdosphincter of the urethra, which corresponds to an age-related decrease in maximal urethral pressure [168]. Thus, in humans, aging may be accompanied by structural LUT changes, including bladder fibrosis and decreased functional musculature in the bladder and urethra [169] (Fig. 2.8).

### **Biochemical and Receptor Alterations with Aging**

The influence of age on muscarinic receptor density and sensitivity has been investigated in animal models with partly conflicting results. Age-related changes in muscarinic receptor function have been reported, but in vitro studies with bladder tissue from old vs. young rats have yielded contradictory results that partly may be strain specific. For example, in Fischer 344 rats, muscarinic receptor-mediated detrusor contraction was either increased [170], unchanged [171, 172], or decreased [162, 173]. In Wistar rats [161, 174], unchanged muscarinic receptor-mediated bladder contraction was reported. However, many studies in Sprague–Dawley rats have demonstrated decreased muscarinic receptor-mediated detrusor contractions [175–177]. In a study of estrogen on older rats, Watanabe et al. [178] found that M2 receptor mRNA expression, but not M3 receptors, was significantly upregulated in older animals. This finding was corroborated by an increased voiding frequency in these two groups elicited by muscarine. Whatever age-related changes in muscarinic receptor functions have been demonstrated in animal bladder, they do not seem to be predictive for what is occurring in humans. Particularly, they do not seem to be associated with a change in the response to antimuscarinics, for there is no evidence for reduced therapeutic benefits from such treatment in older adult patients [179, 180].

A study by Mansfield et al. [181], using radioligand-binding assay, showed that the total number of muscarinic receptors in the human male detrusor decreased with age. This study also found a decrease in mRNA expression of M3





**Fig. 2.8** Light microscopy picture from human detrusor muscle. This image shows a combined muscle cell, collagen (yellow), and elastin stain (original magnification  $\times 150$ ).

(a) Normal detrusor, (b) Male with prostatic obstruction, (c) Elderly female without LUTS. From: Nordling J. *Exp Gerontol.* 2002 Aug-Sep;37(8, 9):991–9

receptors with age in both male and female subjects, but no change in M2 receptors. Due to the lack of highly specific antibodies for the muscarinic receptor subtypes, it was not possible to decide if these changes in mRNA expression were accompanied by a change in protein expression. The functional consequences of the findings were not reported. In contrast to these findings, Wuest et al. [182] found that mRNA detected for M2, M3, P2X1, and P2X3 receptors did not change with age.

The mRNA expression of the purinergic P2X1 receptor was negatively correlated with age in samples of detrusor muscle from normal control male individuals. This negative association was not observed in samples from obstructed patients [183]. Yoshida et al. [184, 185] found a significant positive correlation between age and the purinergic component of human bladder preparation contraction and a significant negative correlation

between age and the cholinergic component of human bladder preparation contraction [140]. The authors studied the neurotransmitter release from the detrusor during electrical field stimulation (EFS), using high-performance liquid chromatography. They found that acetylcholine release and age were significantly negatively correlated, while ATP release and age were positively correlated. In the guinea pig, aging decreased the neurogenic contraction of isolated detrusor induced by EFS, but did not alter the cholinergic component of the contraction [186]. Contractile properties or excitability of human detrusor muscle preparations from normal individuals did not vary with age, but declined in pathological conditions such as bladder outlet obstruction and idiopathic or neurogenic detrusor overactivity [187]. Wuest et al. [182] studied the putative age-dependence of concentration-response curves to the muscarinic agonist carbachol and the purinergic

agonists ATP and  $\alpha$ - $\beta$  methylene-ATP in human detrusor muscle strips. They found, in accordance with the results of Yoshida et al. [184] that the sensitivity to  $\alpha$ - $\beta$  -methylene-ATP increased with age. However, patient age did not influence (1) EFS evoked contractions and the effects of several antimuscarinic drugs, (2) concentration-response curves for carbachol and their modulation by antimuscarinic agents, and (3) expression levels of receptor subtype mRNA. It was concluded that there was no evidence for age-related contractile deterioration in the detrusor. This is in contrast to findings in functional in vivo studies in humans (see below).

### Functional Micturition Changes with Aging

The aging process of both genders is associated with significant changes in bladder function and clinical symptomatology. However, the pathophysiology behind the dysfunctions is sometimes difficult to establish, since it is often difficult to separate what can be attributed to “normal aging” from what is caused by comorbidities. LUTS are divided into storage (irritative), voiding (obstructive), and postmicturition components. Storage symptoms are urgency, frequency, nocturia, and urgency incontinence; voiding symptoms include a reduced force of stream, hesitancy, inability to empty the bladder, and straining and postmicturition symptoms include feeling of incomplete emptying and postmicturition dribble [188]. Unfortunately, none of these symptoms is disease specific or has a high correlation to a specific urodynamic pattern. Most of these symptoms have been suggested to be age dependent and attributed to various factors including reduced bladder capacity, changes in bladder sensation, and DO. Early uroflow studies demonstrated an age-dependent decrease in  $Q_{\max}$  [189, 190], which was confirmed and shown to be similar in both sexes [168, 191], however, not demonstrable in symptomatic elderly men with nonobstructive voiding dysfunction [192].

Detrusor underactivity [193, 194], leading to emptying difficulties and symptoms sometimes

overlapping with those of detrusor overactivity, may have many underlying causes. Some of the most frequently discussed are impaired detrusor contractility and decreased sensation [195]. Urodynamic assessment in older patients of both sexes without overt neurological disease showed higher residual volumes and lower detrusor shortening velocities, but no changes in isometric detrusor function [196]. In a series of patients, where the bladder capacity at first void was taken as measure of bladder sensation, this parameter showed a progressive increase with age, suggesting an age-dependent decrease in bladder sensation [197], a finding confirmed by several other investigators [159, 168]. In a clinical study of patients referred for LUTS or UI, Madersbacher et al. [191] found an increase in postvoid residual volume, along with a decrease of flow rates, voided volumes, and bladder capacity associated with increasing age. These findings were similar in both genders. Pfisterer et al. [168] assessed a group of 85 female volunteers aged between 20 and 90 years with a bladder diary, uroflowmetry, and detailed videourodynamics. Bladder capacity did not change with age, but was smaller in women with detrusor overactivity (DO) on urodynamics. Urine production and urine frequency did not differ significantly with age. Bladder sensation, detrusor contraction strength, maximal flow rate, and maximum urethral closure pressure were all negatively associated with age. It was concluded that there is a normal functional decline seen with aging in otherwise asymptomatic women. This study suggested a progressive decrease in detrusor contraction strength, which was in line with the findings of van Mastrigt [198], who demonstrated a statistically significant age-related decrease of the detrusor contractility parameter,  $W_{\max}$ , in both sexes. Other investigators were unable to show any correlations between bladder contractility and age in symptomatic elderly men with nonobstructive bladder dysfunction [192] or between either maximum detrusor pressure or detrusor pressure at peak flow rate and age in LUTS patients of both sexes [191].

Normal age-related changes in the bladder and lower urinary tract should be clearly differentiated from pathological alterations seen with

conditions such as OAB or LUTS. Detrusor underactivity and the related condition, “detrusor hyperactivity with impaired contractile function” (DHIC) [199] can also present with advancing age and should be diagnosed adequately in elderly individuals. The current available data from animal and human studies demonstrate that aging impacts the lower urinary tract function through ultrastructural and physiological alterations. The reported age-related changes in animals do not always correspond to what is found in humans and should be interpreted with caution. Overall, in humans, bladder sensation and contractility seem to decrease with advancing age as a possible consequence of neuronal loss and remodeling of the bladder and urethra.

## Bladder Summary

Changes in bladder structure and function are common with advancing age. These can influence a wide variety of features in older patients including how they sense bladder fullness, whether they experience urinary urgency frequency, and the volume of urine they are able to hold. In addition, these changes can have significant effects with regard to urinary incontinence and bladder emptying efficiency. Identification of many of these changes has led to targets for therapy, particularly for OAB and urge urinary incontinence. Additional work will help to better define additional changes associated with bladder aging and may lead to new therapies in the future.

## Conclusions

Studies in molecular and cellular biology, biochemistry, physiology, and biophysics have dramatically advanced our understanding of the genitourinary system across the human lifespan. Basic science and translational research hold the key to future advances in this field, including identification and development of new targets for clinical therapies. This chapter has focused on disease processes of the prostate and bladder, but similar advances have been made in other fields

including kidney diseases, urolithiasis, sexual dysfunction, and urinary tract infection. Additional basic science concepts are addressed in other chapters as they relate to specific disorders of the aging genitourinary system. Future research will certainly help advance the science and subsequent clinical care for older adults.

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