Prostate Physiology:

The Most Diseased Male Organ?

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Disclosure of Financial Relationships

Ryan P Terlecki, MD, FACS

Has disclosed relationships with an entity producing, marketing, re-selling, or distributing health care goods or services consumed by, or used on, patients.

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Research Grants/Contracts

AMS/Boston Scientific

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Department of Defense

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Objectives (in 20 minutes)

- Provide an overview of relevant prostatic anatomy and physiology
- Discuss the data regarding association between inflammation and BPH/PCa
- Review data regarding the prostate microbiome and potential influence on disease

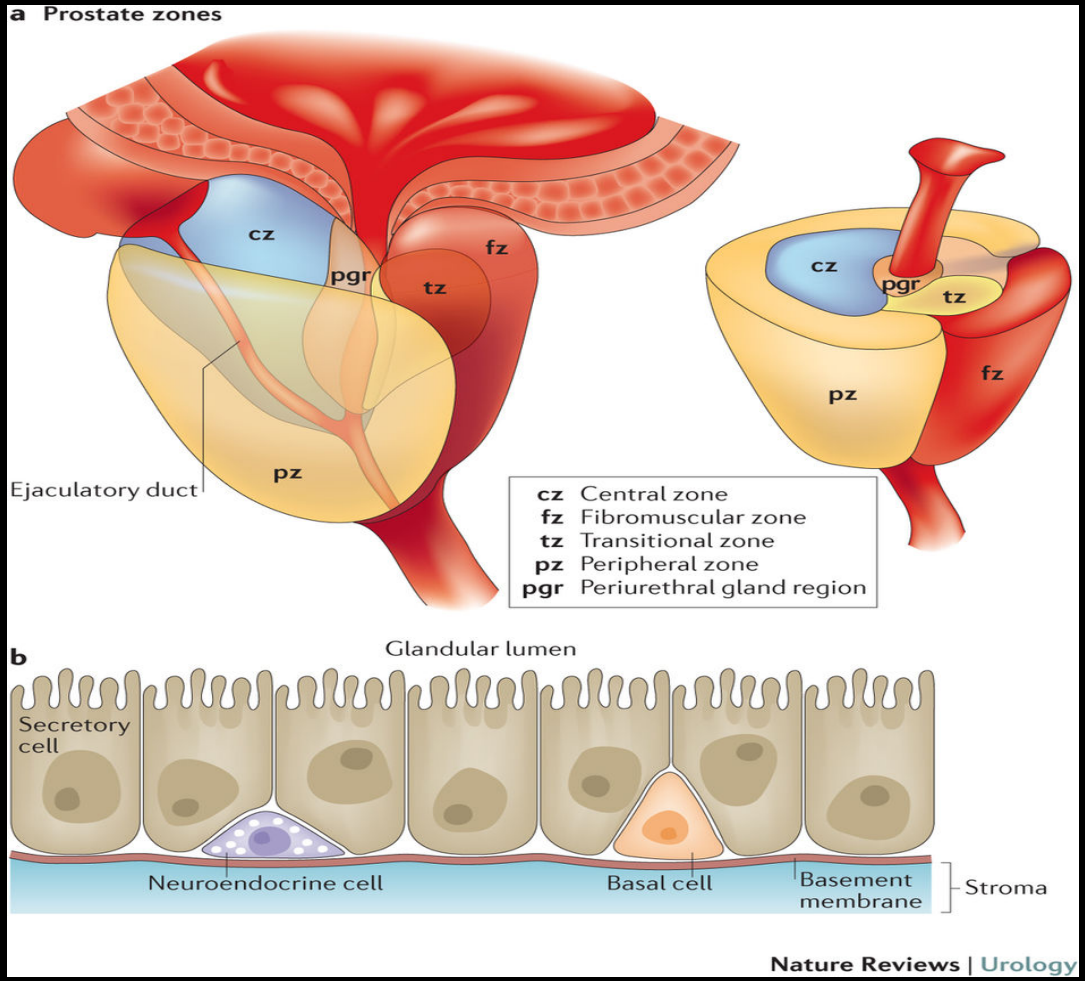
Audience Response Question 1

Audience Response Question 2

Physical Structure

- First described by Lowsley as having 5 lobes (unlike rat, humans have distinct zones within a uniform gland)
- Organized like a bunch of grapes (like alveoli) in fibrous gelatin
- Cell types
  - Secretory epithelial cells (tall columnar)
  - Basal/stem cells (cuboidal epithelial)
  - Neuroendocrine cells
  - Stromal (SMCs, fibroblasts, endothelial)

Lowsley OS. Am J Anat 1912. 13:299-349


a Prostate zones
cz
pgr
fz
tz
pz
Ejaculatory duct
cz Central zone
fz Fibromuscular zone
tz Transitional zone
pz Peripheral zone
pgr Periurethral gland region
b
Glandular lumen
Secretory cell
Neuroendocrine cell
Basal cell
Basement membrane
Stroma
Nature Reviews | Urology

Stroma and tissue matrix

- Stroma separated from the cellular components by a basement membrane composed of extracellular matrix
- Important for structural organization, but also has role in development and control of cellular functions
- Appears to have a pivotal role in the prostate inflammatory response

Nieto et al. Endocr Relat Cancer 2014. 21:T147-T160

Who needs a prostate anyway?

- Essential for fertility
- Role as trigger for ejaculation, sperm activation, and capacitation
- Prostate epithelial cells are the only healthy human cells that produce energy by glycolysis rather than the Krebs cycle

Verze et al. Nature Reviews Urology 2016. 13:379-386

Prostatic Fluid

- KLKs (esp KLK2 and KLK3=PSA, discovered 1979)
- Citrate
- Zinc: prostate w/**highest levels of any soft tissue**
- Spermine: may protect from infection
- Prostaglandins: **misnomer**; more in SVs
- Cholesterol: stabilize spermatozoa
- Seminin: affects liquefaction; odor source
- Acid Phosphatase: Old urologists (**Crawford**) used this

Wang et al. Invest. Urol 1979. 17:159-163
Huggins, C. Harvey Lect 1947. 42:148
Frick and Aulitzky. Infection 1991. 19 suppl 3:S115-118

Zinc

- Accumulated within epithelial cells (4% of body content); possibly supported by prolactin
- Blocks Kreb cycle and causes citrate accumulation (which is the energy substrate for sperm)
- Causes temporary inactivity of KLKs
- Major Zn transporter (Z1P1) decreased or absent in PCa tissue compared to normal or BPH tissue (hypothesized tumor suppressor)

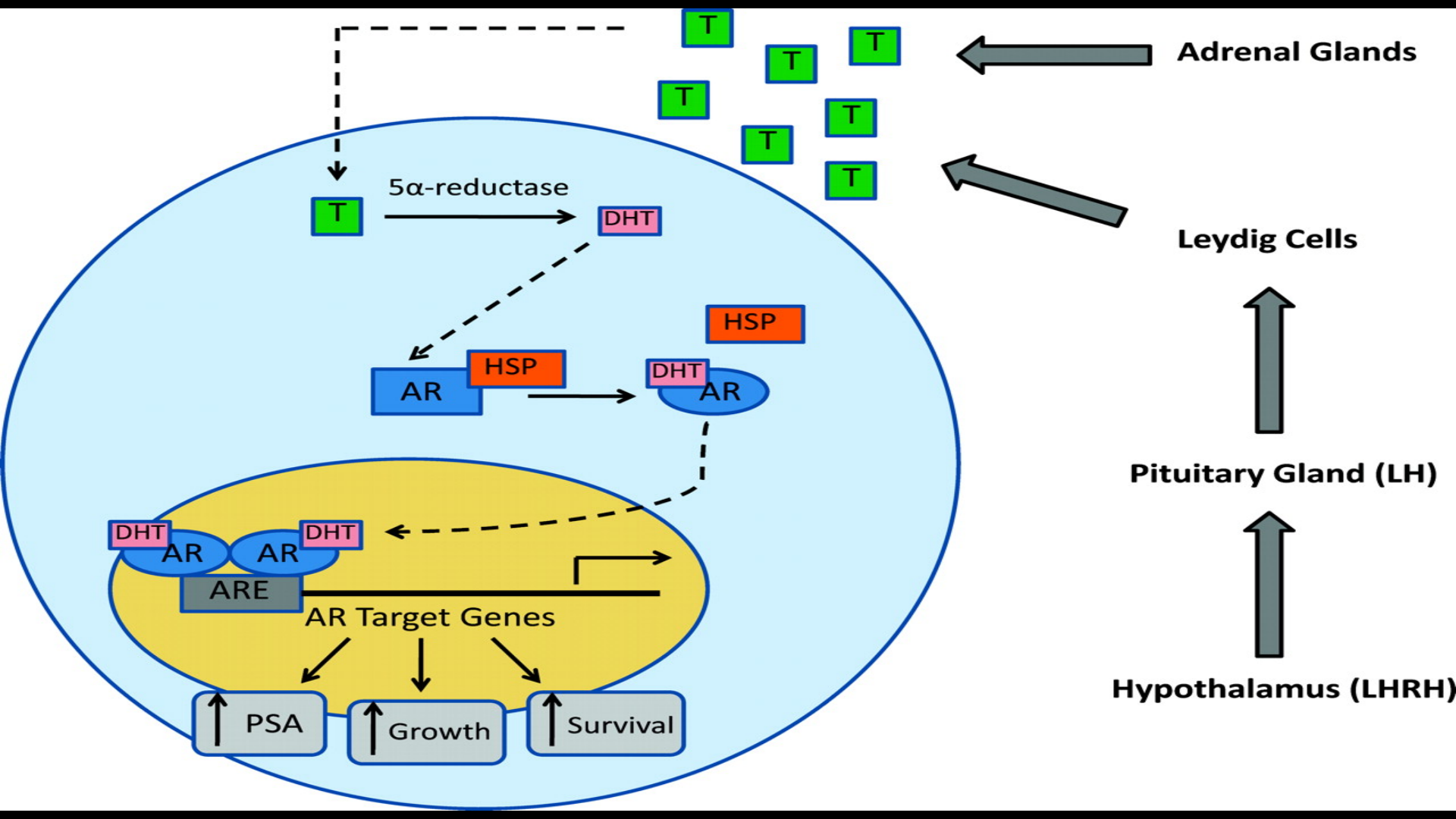
Wang et al. Invest. Urol 1979. 17:159-163
Huggins, C. Harvey Lect 1947. 42:148
Frick and Aulitzky. Infection 1991. 19 suppl 3:S115-118
Verze et al. Nature Reviews Urology 2016. 13:379-386

Hormonal Control

- 98% of testosterone in blood is bound to protein (mainly albumin and SHBG)
- Only 2% of circulating testosterone is available to enter prostate via diffusion from plasma
- Over 95% of testosterone converted to DHT (flatter, higher binding affinity than T)
- DHT binds AR and complex goes to nucleus

Androgen Metabolism of Prostate

- RNA polymerase activated, mRNA synthesized (transcription)
- Ribosomal translation of mRNA results in production of cytokines (EGF, FGF, PDGF) and secretory proteins (enzymes)
- Cytokines stimulate cell growth via receptors on epithelial and stromal cells
- Proteins are secreted into lumen on neurological command during ejaculation


T
T
T
T
T
T
T
Adrenal Glands
Leydig Cells
5α-reductase
T
DHT
HSP
AR
HSP
DHT
AR
Pituitary Gland (LH)
DHT
AR
AR
DHT
ARE
AR Target Genes
Hypothalamus (LHRH)
PSA
Growth
Survival

Androgen Regulation

- AR gene is a master gene in prostate physiology; two forms (A,B) can be transcribed but no evidence of different roles
- Expression essential for epithelial homeostasis (>300 AR mutations in PCa lines)
- With age, T/DHT decrease, gland function is impaired, reducing ability to maintain healthy levels of Zn, citrate, KLK (fertility goes down and weakens ability to inhibit Krebs cycle—favors cancer-prone status)

Androgen Regulation

- Prostate doesn’t grow in prepubertal castrates (eunuch studies)
- Castration causes gland regression in mature males by apoptosis, reversible with androgen replacement (female embryos exposed to androgens will develop prostates)
- Estrogens act **in concert** with androgens to promote and inhibit growth (alpha, beta)

Innervation

- Adrenergic and noradrenergic generally well known by providers (think about BPH meds)
- Evidence for M1 receptors on epithelium, M2 on stroma, and M1 + M3 in some cancer cell lines
- Data suggests these receptors may modulate PCa growth, with cholinomimetics contributing to proliferation

Ventura et al. Pharmacology & Therapeutics 2002. 94:93-112

Immunoactivity

- Immunocompetent organ (like lung, intestine)
- Populated by lymphocytes, macrophages, and mast cells
- Immune responses in prostate tissue likely influenced by sex hormones, which can affect susceptibility to inflammation

Immunoactivity

- Lymphocytes secrete cytokines
- Cytokines regulate (paracrine and autocrine) stromal and epithelial cell growth
- Think of **clinical associations**
  - Estrogen is pro-inflammatory
  - Obesity associated with higher E2 and higher inflammation (metabolic syndrome)
  - Some suggest LUTS improve with reductions in obesity

The Clinical Burden

- #1 nonskin CA, #2 CA killer (after lung)
- Autopsy data shows invasive cancer in 64% of men approaching 70 years of age
- BPH most common urologic disease in older men (25% in 50s, 33% in 60s, nearly 50% in 80s)

Jemal et al. CA Cancer J Clin 2010; 60:277-300
Kramer et al. Eur Urol 2007; 51:1202-16
Robert et al. Eur Urol Suppl 2009; 8:879-86
Sakr et al. In Vivo 1994. 8(3):439-43

PCa and BPH

- Form in different areas of the prostate (generally)
- Considered chronic diseases with slow progression
- Prevalence rises with age, both are hormone dependent, and both have been associated with inflammation

Prostatitis

- Prevalence of 5-13%, >2 million hospital visits per year in US, seen in >78% of men in REDUCE trial
- Acute bacterial, chronic bacterial, inflammatory, noninflammatory, asymptomatic
- Suggested to be causative in pathology of BPH as early as 1937

Rao et al. Prostate Cancer Prostatic Dis 2002. 5:172-179
Moore D. J Urol 1937. 38:173-82

Prostatitis and Cancer

- California Men's Health Study
  - 68,675 men
  - Prostatitis 1.30 RR for PCa
  - Longer duration, higher risk (p = 0.003)

- Association deemed significant based on meta-analysis of 20 studies

- Daily intake of NSAIDs (primarily ASA) has been associated with a 39-66% risk reduction for PCa

Cheng et al. PloS One 2010. 5(1):e8736
Jiang et al. PLoS One 2013. 8(12):e85179
Harris et al. Oncol Rep 2005. 13(4):559-83
Nelson and Harris. Oncol Rep 2000; 7:169-70

Prostate Microbiome

- Analysis now feasible through molecular-based assays
- The prostate is not a sterile environment and bacterial populations may differ between benign and malignant tissue
- Unclear ‘which promotes which’

Cavaretta et al. Eur Urol. 2017;72:625-631

Infection Causing Cancer?

- Virchow 1863; Also consider example of Helicobacter pylori
- First proposed for PCa in the early 1950s
- Some association between PCa risk and gene variants of COX-2, RNASEL, and TLR4 identified in cases of hereditary PCa
- RP specimen analysis shows over 70% contain *Enterobacteriaceae*

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Yow et al. Infect Agent Cancer 2017. 12:4

Propionibacterium acnes

- Abundant within prostate tissue, vaginal tissue, and frequently found in urine; population increased by testosterone use
- Proinflammatory role; Has been associated with PCa and been found absent in normal tissue; **Suggested as initiator or promoter**
- Reported in **78-95% of PCa specimens and 100% of PIN lesions**; predictive of CA on subsequent biopsies for elevated PSA

Cavaretta et al. Eur Urol. 2017;72:625-631
Cohen et al. J Urol. 2005; 173:1969-1974
Alexeyev et al. J Clin Microbiol. 2007; 45:3721-3728
Yow et al. Infect Agent Cancer 2017. 12:4
Fehri et al. Int J Med Microbiol 2011. 301:69-78
Kiraly et al. Acta Derm Venereol 1988; 68(1):21-6

Audience Response Question 1

Audience Response Question 2

Conclusions

- The prostate is an immunocompetent, androgen-dependent organ of fertility, but the direct target for a number of benign and malignant diseases
- Impairment of the status of the epithelium can decrease accumulation of Zn and citrate, and affect KLK secretion
- Inflammation associated with both BPH and PCa but data cannot truly confirm causality

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