Biophysiology of BPH: Pathogenesis

Seoul National University Hospital

Cheol Kwak
Cellular changes in BPH

**Stromal Elements:** increased stromal mass (particularly, amount of smooth muscle cells)

“reawakening” of embryonic mesenchyme

↑ fibroblasts/fibromuscular components

↑ nonmuscle myosin heavy chain (NMMHC)

↓ smooth muscle myosin heavy chain (SMMHC)

↓ elastin (reduced elastic tissue)

**Local autonomous nervous system**
Morphological characteristics of BPH

- Budding of epithelium from preexisting ducts -> new architecture
  central feature of embryonic development / repressed in adult life

- Earliest manifestation of BPH: appearance of mesenchymal in
  periurethral nodules \(\rightarrow\) reminiscent of embryonic mesenchyme
  • BPH - intrinsically mesenchymal disease and resulting from
    reawakening of embryonic inductive interactions between
    prostatic stroma and epithelium (McNeal, 1990)

- Comparison of fetal prostatic stroma and BPH stroma (Bierhoff et
  al, 1997): Ontogenetic processes is recapitulated in BPH
  development, supporting theory of embryonic “reawakening” in
  BPH pathogenesis
Changes of autonomous nervous system in aging prostate

Neuronal systems with effects on prostate

- $\alpha$-adrenergic
- $\beta$-adrenergic
- Cholinergic
- Peptidergic
- ↓ Enkephalinergic (mediating smooth muscle cell relaxation)
- ↓ Nitrinergic system (mediating smooth muscle cell relaxation)
  nNOS ↓ in BPH TZ vs. iNOS ↑ in BPH stroma d/t increased pro-inflammatory condition in BPH
$\alpha_1$-adrenergic receptor subtypes

![Diagram of $\alpha_1$-adrenergic receptor subtypes]

- $\alpha_1$
  - $\alpha_1a$
    - $\alpha_1a-1$
    - $\alpha_1a-2$
    - $\alpha_1a-3$
    - $\alpha_1a-4$
  - $\alpha_1b$
  - $\alpha_1d$

"Wild type"
Tissue distribution of $\alpha_1$-adrenergic receptor subtypes

$\alpha_1$ARs and Human LUTS

- **Prostate**
  - Smooth muscle contraction
  - $\alpha_{1a}$

- **Spinal cord**
  - Lumbosacral
  - $\alpha_{1d} > \alpha_{1a}$, $\alpha_{1b}$

- **Detrusor**
  - Instability
  - Irritative symptoms
  - $\alpha_{1d} > \alpha_{1a}$

- **Vessels**
  - Resistance vessels
  - $\alpha_{1a}$
  - Ageing effects
  - $\alpha_{1b} > \alpha_{1a}$

---

NET:
- Target $\alpha_{1d}$/$\alpha_{1d}$ (Therapeutic effect-men)
- Target $\alpha_{1d}$ (Therapeutic effect-women)
- Avoid $\alpha_{1b}$ (Cardiovascular homeostasis in elderly)
**Cellular changes in BPH**

**Epithelial Elements**

A. Luminal cells
   - Flatten
   - ↑ intraluminal space
   - ↑ Vimentin (mesenchymal marker)
   - ↓ PSMA
   - ↓ α1-antichymotrypsin (maybe related to PSA elevation in BPH)
   - ↓ α1b-adrenergic receptor

B. Basal cells: hyperplasia (enlarged, hypertrophic)
   - Attenuated
   - ↓ keratin 5 (basal cell marker)
   - ↓ Cellular adhesion molecule expression (e.g. C-CAM)

C. Neuroendocrine cells
   - ↓ Numbers
   - ↓ Overall innervation
**BPH alterations in molecular signaling**

**Hormones:** local endocrine system
- $\uparrow$ 5-$\alpha$-reductase activity (stromal cells)
- $\uparrow$ 17-β-hydroxysteroid dehydrogenase

- $\uparrow$ nuclear androgen receptors (basal epithelium)

- $\uparrow$ androgen receptor co-activators (e.g., ARA54, ARA55, SRC1) (Mestayer et al, 2003)
- $\downarrow$ androgen co-repressor (DAX-1) (Agoulnik et al, 2003)
Local sex-steroid hormone metabolism and regulation

- Prostatic bioavailable testosterone levels: ↓ with age
- Prostatic E2/bioavailable T ratio: ↑ in BPH - estrogens in smooth muscle cell growth and differentiation?
  - ER-α in stromal cells / ER-α and ER-β in basal epithelial cells - both upregulated in BPH basal cells (Royuela et al, 2001)
  - Anti-estrogens and aromatase inhibitors for medical treatment of BPH - disappointing phase-III randomized clinical trials with aromatase-inhibitors (Sciarra and Toscano, 2000)
- DHT required by luminal secretory cells for terminal differentiation and secretory function
DHT production and action in prostate
Prostatic imbalance between cellular proliferation and cellular death hypothesized to underlie BPH
BPH alterations in molecular signaling

Growth Factors
↑ FGFs (e.g., FGF-1, -2, -7, -9)
↑ HIF-1
↑ Insulin growth factors (e.g., IGF-2)
↑ IGFRs (e.g. IGF-I-R)
↑ VEGF
↓ IGF down-regulators (e.g., WT-1, IGFBP-2)

Cytokines: including infiltrating cells of immune system
↑ Interleukins (e.g., IL-1α, -2, -4, -8, -15, -17)

Others
↑ MAPK (e.g., ERK, p-38)
↑ Angiotensin converting enzyme activity
↓ Thrombospondin-1
Growth factors (FGFs) and cytokines

- Mitogenic activities of FGF-1, 2 and 7 on stromal and/or epithelial cells: consistent with growth promoting role in BPH
- FGFs: produced for the most part by stromal cells, with some small amount of FGF-2 by epithelial cells → autocrine and paracrine

- Local hypoxia → HIF-1 ↑ → hypoxia responsive gene activation → FGFs (Berger et al, 2003)

Double paracrine loop !!
Increased tissue mass in BPH
Growth factors (TGF) - 1

- TGF-β: implicated in BPH and one example of cellular complexity of BPH
- Differentially affecting growth of normal and BPH stromal cells, possibly via differential regulation of IGFBPs.
  - IGFBP-3 expression ↑15-fold in normal cells but ↑2-fold in BPH cells when exposed to TGF-β1: associated with overall inhibition of 60% of growth in normal cells compared to 20% in BPH cells (Cohen et al, 2000)
- TGF-β primarily in secretory epithelial cells of BPH / higher expression in BPH (Kyprianou et al, 1996)
  - TGF-β2, but not TGF-β1, ↑ in BPH (Mori et al, 1990)
Epithelial secretion of TGF-β: regulating stromal cell response in BPH pathogenesis

- TGF-β1 low concentration - supporting proliferation, high-inhibiting prostate stromal cell growth (Kassen et al, 1996)

Transdifferentiation of prostatic fibroblasts into myofibroblasts/SMCs upon TGF-β1 (Peehl and Sellers, 1997; Rumpold et al, 2002)

- TGF-β1 into human prostatic stromal cell culture: inducing overexpression of SMC-α-actin, calponin and tenascin (markers for myofibroblasts/SMCs) in prostate stroma; generating ‘reactive stroma’ composed of myofibroblasts and fibroblasts expressing ECM components (Peehl and Sellers, 1997; Rumpold et al, 2002; Tuxhorn et al, 2002)
Luminal/epithelial cell interactions

- BPH development accompanied by occurrence of corpora amylacea and prostatic calculi (Geramoutsos et al, 2004)
- Prostatic calculi: exacerbating LUTS / clogging prostatic ducts, obstructing prostatic acini, initiating inflammatory reactions and causing abscesses (Klimas et al, 1985; Sondergaard et al, 1987)
- Frequent drainage of prostate fluid: stop formation of tiny crystalloid microcalcifications in prostate ducts and preventing accumulation of substances that harm epithelia within clogged ducts (Leitzmann et al, 2004)
- TGF-β1 stimulation of BPH basal epithelial cells → differentiation of vimentin (+), SA-β-gal (+) and hypertrophic epithelial cells (Untergasser et al, 2003)
- ↑ vimentin expression (Fraga et al, 1998) and ↑ SA-β-gal activity in hypertrophic BPH basal epithelial cells (Choi et al, 2000)
Conclusions

- Cellular interactions between epithelial and stromal elements: important in BPH
- Autocrine and paracrine pathways through stromal cells: focal areas for reawakening of epithelial budding and subsequent BPH nodule formation
- Identification of numerous gene products and growth factors associated with BPH through genetic arrays and primary cell culture models: focus of continued research
- Heterogeneous nature of BPH tissue → selective LCM etc.
- Paradigm of balanced cellular growth with apoptosis and senescence: novel areas such as senescence and BPH-specific biomarkers
- No single pathomechanism, but **synergistic effect of multiple events** within biological communication systems (nerve-, endocrine-, immune system) during aging process of prostate