

The Molecular Pathogenesis of Human Prostate Cancer

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Introduction

Prostate cancer (PCA) has become the most commonly diagnosed cancer among men in the USA, with an estimated 189,000 cases diagnosed in 2002 (1). Encouragingly, over the past several years, increased use of serum prostate-specific antigen (PSA) screening has increased the fraction of men diagnosed with PCA confined to the prostate gland, leading to more effective use of surgery and radiation therapy for treatment, and to a decline in PCA mortality (2, 3). Despite these improvements, some 30,200 men will likely die of progressive metastatic cancer in 2002 (1). Furthermore, even though men with early PCA can be cured using surgery or radiation therapy, the side effects of treatment frequently include erectile dysfunction, urinary incontinence, or rectal irritation (4-6). New insights into the etiology of PCA are needed so that new strategies for its prevention can be developed.

Recent studies of the earliest molecular steps in the development of human PCA have generated new evidence supporting causative roles for prostate inflammation and diet in prostatic carcinogenesis. These new findings have provided new clues as to how PCAs likely arise, and new insights into how the disease might be prevented. A new lesion, termed proliferative inflammatory atrophy (PIA), in which prostate epithelial cells undergo regenerative proliferation in response to inflammatory damage, appears to be a precursor to prostatic intraepithelial neoplasia (PIN) and to PCA (7). PIA lesion cells exhibit many signs of stress, including the induction of carcinogen-detoxification enzymes such as glutathione S-transferases *GSTA1* and *GSTP1* (7). Somatic inactivation of *GSTP1*, encoding the human π -class GST, renders prostate epithelial cells vulnerable to suffer genome damage mediated by reactive chemical species generated by inflammatory cells, or ingested as part of the diet (8). By leading to more somatic genome alterations, loss of *GSTP1* function leads to PIN or PCA.

Thus, *GSTP1* likely acts as a “caretaker” gene in the prostate (9). When induced, as in PIA lesion cells, it affords protection against cell and genome damage; when its function is lost, genomic instability, driven by genome damage, ensues. New PCA prevention strategies can target this vulnerability to genome damaging, perhaps by attenuating prostatic inflammation, buttressing carcinogen defenses, or by both approaches.

PCA Epidemiology: Prostate Inflammation and Diet

PCA is a disease of Western lifestyle. PCA incidence and mortality are known to vary widely between different geographic regions, with high rates in the USA and Western Europe, and low rates in Asia (10). Asian immigrants to North America adopt higher PCA risks, especially after more than 25 years exposure to a Western lifestyle, and Asian men born in North America have high PCA risks (11-13).

Chronic (or recurrent) prostatitis is one etiological factor that is increasingly suspected to lead to PCA (14). Prostate inflammation is ubiquitously present in prostates removed by radical prostatectomy for PCA in the USA, however, the prevalence and age distribution of asymptomatic prostatitis, in the USA, or elsewhere, is not known. About 9% of men between 40 and 79 years of age report suffering of symptomatic prostatitis, with half of them having repeated episodes (15-17). Although many of these inflammations may be triggered by infections, the infectious cause is most often not identified. Since prostatitis is so common in the USA, often asymptomatic, and of uncertain etiology, causative associations between prostatitis and PCA have been difficult to assess in epidemiology studies. Despite these limitations, an increased PCA risk has been associated with sexually transmitted infections, independent of the specific pathogen, hinting that the inflammatory response to infection, rather than the infectious agent itself, may lead to PCA (18, 19). In addition, host responses to prostate infections may underlie some familial PCA clusters. Genetic studies of familial PCA have identified two candidate PCA susceptibility genes, 2'-5'-oligoadenylate-dependent ribonuclease L (*RNASEL*), and macrophage scavenger receptor 1 (*MSR1*). These genes are thought to encode proteins with critical functions in host responses to a wide variety of infectious agents (20-23). Finally, an inflammatory lesion in the human prostate, PIA, may be a precursor to PIN and to PCA (7).

A key feature of Western lifestyle that may promote PCA development is the diet. Several epidemiology studies have implicated various dietary components, such as animal fat and charred meat, rich in the Western diet, as high PCA risk factors; while vitamins, fruits, and vegetables, poor in the Western diet, as dietary factors that decrease PCA risk (24-31). However, whether the high PCA risk diet represents an error of *commission* (i.e., over-consumption of animal fats and charred meats), *omission* (i.e., under-consumption of fruits and vegetables), or *both*

has not been proven. Nevertheless, there are carcinogens present in the Western diet. Male rats fed the heterocyclic aromatic amine 2-amino-1-methyl-6-phenylimidazo[4,5- β] pyridine (PhIP), an intermediate metabolite formed while preparing “charred” or “well-done” meat, develop DNA mutations in prostate cells that result in PCAs (32, 33).

Somatic Genome Alterations in PCA Cells

Autopsy studies suggest that PCA begins in USA men at quite a young age. Small cancer foci have been reported in about 29% of men aged 30-40 years (34). Not surprisingly, by the time the disease is diagnosed, age 60-70 years, the DNA of the neoplastic cells has accumulated a large number of somatic genome alterations, including gene mutations, amplifications, and deletions, chromosomal rearrangements, and changes in DNA methylation (Figure 1). Not only a large number of somatic genome alterations arise in each individual PCA patient, but among different PCA patients, and between different PCA lesions from a single patient, indicating a striking heterogeneity of genome changes. This suggests that the alterations may arise as a consequence of prolonged exposure to genome damaging stresses, such as those associated with inflammation or ingestion of heterocyclic amine carcinogens, given rise to poor maintenance of genome integrity, by either one of these processes or both.

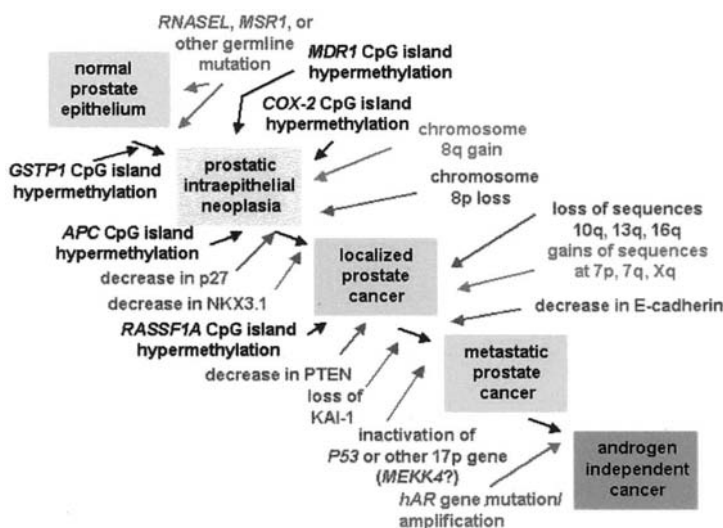


Figure 1. The molecular pathogenesis of human PCA: *GSTP1* CpG island hypermethylation initiates prostatic carcinogenesis.

Table 1. *GSTP1* CpG Island Hypermethylation in Prostate Cancer.

| Study | Detection Technique | Results |
|----------------------------------|--|--|
| Lee, <i>et al.</i> (36) | SB ¹ | Tissue: 100% PCA ⁵ , 0% BPH ⁶ |
| Lee, <i>et al.</i> (49) | RE-PCR ² | Tissue: 91% PCA ⁵ |
| Brooks, <i>et al.</i> (38) | RE-PCR ² | Tissue: 70% PIN ⁷ |
| Santourlidis, <i>et al.</i> (50) | RE-PCR ² | Tissue: 75% PCA ⁵ , 0% TCC ¹⁰ |
| Millar, <i>et al.</i> (51) | BGS ³ | Tissue: 83% PCA ⁵ |
| Suh, <i>et al.</i> (52) | RE-PCR ² | Ejaculate: 44% PCA ⁵ |
| Goessl, <i>et al.</i> (53) | MS-PCR ⁴ | Tissue: 94% PCA ⁵ , 0% BPH ⁶ Plasma: 71% PCA ⁵ Ejaculate: 50% PCA ⁵ |
| Goessl, <i>et al.</i> (54) | MS-PCR ⁴ | Urine: 73% PCA ⁵ , 29% PIN ⁷ , 2% BPH ⁶ |
| Cairns, <i>et al.</i> (55) | MS-PCR ⁴ | Tissue: 79% PCA ⁵ Urine: 27% PCA ⁵ |
| Lin, <i>et al.</i> (37) | SB ¹ , RE-PCR ² , BGS ³ | Tissue: 100% PCA ⁵ |
| Goessl, <i>et al.</i> (56) | MS-PCR ⁴ | Tissue: 90% PCA ⁵ , 0% BPH ⁶ Plasma: 72% PCA ⁵ Urine: 76% PCA ⁵ Ejaculate: 50% PCA ⁵ |
| Jeronimo, <i>et al.</i> (57) | MS-PCR ⁴ | Tissue: 91% PCA ⁵ , 54% PIN ⁷ , 29% BPH ⁶ |
| Chu, <i>et al.</i> (58) | MS-PCR ⁴ | Tissue: 100% PCA ⁵ , 7% BPH ⁶ |
| Jeronimo, <i>et al.</i> (59) | MS-PCR ⁴ | Tissue: 91% PCA ⁵ , 29% BPH ⁶ Urine/Plasma: 54% PCA, 3% BPH ⁶ |
| Goessl, <i>et al.</i> (60) | MS-PCR ⁴ | Prostate Biopsy Washings: 100% PCA ⁵ , 67% PIN ⁷ , 0% BPH ⁶ |
| Harden, <i>et al.</i> (61) | MS-PCR ⁴ | Tissue: 73% PCA ⁵ , 0% BPH ⁶ |
| Gonzalogo, <i>et al.</i> (62) | MS-PCR ⁴ | Post-Biopsy Urine: 58% PCA ⁵ , 33% non-PCA, 67% atypia/PIN |
| Nakayama, <i>et al.</i> (63) | MS-PCR ⁴ | Tissue (LCM⁸): 91% PCA ⁵ , 69% PIN ⁷ , 6% PIA ⁹ , 0% normal |
| Gonzalogo, <i>et al.</i> (64) | MS-PCR ⁴ | Prostate Secretions: 76% PCA ⁵ |

¹ SB, southern blot analysis ² RE-PCR, methylation-sensitive restriction enzyme-PCR³ BGS, bisulfite genomic sequencing⁴ MS-PCR, methylation-specific-PCR⁵ PCA, prostate cancer⁶ BPH, benign prostate hypertrophy⁷ PIN, prostate intraepithelial neoplasia⁸ LCM, laser capture microdissection⁹ PIA, proliferative inflammatory atrophy¹⁰ Transitional cell carcinoma

GSTP1, encoding the π -class GST, likely acts as a “caretaker” gene in the prostate, preventing the acquisition of somatic genome changes in response to exposure to genome damaging agents. In mice, targeted disruption of *GSTP* genes leads to an increased susceptibility to skin carcinogenesis after exposure 7,12 dimethylbenz[a]anthracene (DMBA) (35). In the human prostate, *GSTP1* is consistently expressed in normal basal epithelial cells, but not in normal columnar epithelial cells (36, 37). This enzyme expression is highly induced in cells comprising PIA lesions (7). In contrast, cells in PIN lesions or in PCA rarely ever express *GSTP1* (36, 38). In fact, loss of *GSTP1* expression often marks the transition between PIA, PIN, or PCA (7). The lack of *GSTP1* expression can be attributed to somatic *GSTP1* gene “CpG island” DNA hypermethylation, resulting in silencing of *GSTP1* transcription via recruitment of ^{5-m}C-binding domain proteins (37, 39). *GSTP1* “CpG island” DNA hypermethylation is now recognized to be the most common somatic genome change in PCAs (Table 1).

Loss of *GSTP1* “caretaker” function early during prostatic carcinogenesis may link PCA epidemiology with the molecular pathology of PCA. Lack of *GSTP1* activity has been shown to render PCA cells vulnerable to genome damage mediated by the heterocyclic amine carcinogen PhIP (8) and by oxidants (41). In response to oxidative genome damaging stresses, the absence of *GSTP1* leads not only to an increase in oxidized DNA bases in genomic DNA, but also to improved cell survival (41). This form of “tolerance” to oxidative genome damaging stresses is reminiscent of the “oxidation tolerance” exhibited by cells with DNA mismatch repair enzyme deficiency, which are prone to suffer increased oxidized DNA base damage, increased mutations, and decreased cell death following exposure to oxidative stresses (40). In cells with both *GSTP1* and DNA mismatch repair enzyme deficiency, “oxidation tolerance” may lead to an increased vulnerability to mutation and neoplastic transformation upon exposure to oxidative genome damaging stresses, including those inflicted by chronic (or recurrent) inflammation (41).

Proliferative Inflammatory Atrophy (PIA)

GSTP1 is typically expressed at high levels in PIA lesions (7). These prostate lesions are composed of proliferating, atrophic-appearing, prostate epithelial cells that are often juxtaposed to activated inflammatory cells (7). The epithelial cells present are distinct in several ways from the atrophic epithelial cells seen after androgen deprivation or anti-androgen treatment. First, PIA lesions are focal, not diffuse. PIA cells are often proliferating quite actively, rather than lying quiescently. Moreover, the PIA cells show many molecular signs of stress, including induction of *GSTP1*, *GSTA1*, and *COX-2* expression (7, 42, 43). PIA lesions are readily evident in radical prostatectomy specimens containing PCA, often present directly adjacent to PIN lesions or PCA (44). Inflammatory lesions in

other organ sites, including the liver, stomach, and colon, are known cancer precursors. In the prostate, rare PIA lesions exhibit somatic genome alterations, such as *GSTP1* “CpG island” hypermethylation and other changes, reminiscent of PIN lesions and PCAs (63). The mechanism by which PIA cells acquire such changes, particularly *de-novo* hypermethylation of *GSTP1* “CpG islands” DNA sequences, has not been elucidated.

New Opportunities for PCA Prevention

The convergence of PCA epidemiology, indicating a possible role for prostate inflammation, and a significant role for the diet, in PCA development, with molecular pathology, revealing that neoplastic prostate cells may have acquired an increased vulnerability to carcinogen damage, provides an opportunity for the discovery and development of rational new approaches to PCA prevention. Possible strategies include reduced exposure to genome damaging oxidants and other carcinogens, and intake of antioxidant micronutrients, including vitamin E, selenium, and carotenoids such as lycopene, which may be able to intercept reactive oxygen species before they inflict genome damage in the prostate. Administration of anti-inflammatory agents, when distributed into prostate tissues, may reduce oxidant production by prostate inflammatory cells. Consumption of cruciferous vegetables, containing the isothiocyanate compound, sulforaphane, an inducer of GSTs and other carcinogen-detoxification enzymes, may raise carcinogen defenses in the prostate and in other tissues to compensate for acquired defects in *GSTP1* “caretaker” gene function (45-47).

Thus, human PCA itself, featuring ongoing threats to genome integrity associated with prostate inflammation and with high-risk dietary practices, may be the most rational “disease” that needs to be targeted for prevention. To discover and develop new agents to treat prostatic carcinogenesis, new clinical trial strategies featuring new “disease” biomarkers will likely be required. For the near future, the most promising PCA prevention strategies under consideration may be the use of anti-oxidant micronutrients (the SELECT trial) and anti-inflammatory agents (48).

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