

Pathological and Molecular Mechanisms of Prostate Carcinogenesis: Implications for Diagnosis, Detection, Prevention, and Treatment

Angelo M. De Marzo,* Theodore L. DeWeese, Elizabeth A. Platz, Alan K. Meeker, Masashi Nakayama, Jonathan I. Epstein, William B. Isaacs, and William G. Nelson

Departments of Oncology, Pathology, Radiation Oncology, Urology, The Johns Hopkins University School of Medicine, and the Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland

Abstract Prostate cancer is an increasing threat throughout the world. As a result of a demographic shift in population, the number of men at risk for developing prostate cancer is growing rapidly. For 2002, an estimated 189,000 prostate cancer cases were diagnosed in the U.S., accompanied by an estimated 30,200 prostate cancer deaths [Jemal et al., 2002]. Most prostate cancer is now diagnosed in men who were biopsied as a result of an elevated serum PSA (>4 ng/ml) level detected following routine screening. Autopsy studies [Breslow et al., 1977; Yatani et al., 1982; Sakr et al., 1993], and the recent results of the Prostate Cancer Prevention Trial (PCPT) [Thompson et al., 2003], a large scale clinical trial where all men entered the trial without an elevated PSA (<3 ng/ml) were subsequently biopsied, indicate the prevalence of histologic prostate cancer is much higher than anticipated by PSA screening. Environmental factors, such as diet and lifestyle, have long been recognized contributors to the development of prostate cancer. Recent studies of the molecular alterations in prostate cancer cells have begun to provide clues as to how prostate cancer may arise and progress. For example, while inflammation in the prostate has been suggested previously as a contributor to prostate cancer development [Gardner and Bennett, 1992; Platz, 1998; De Marzo et al., 1999; Nelson et al., 2003], research regarding the genetic and pathological aspects of prostate inflammation has only recently begun to receive attention. Here, we review the subject of inflammation and prostate cancer as part of a “chronic epithelial injury” hypothesis of prostate carcinogenesis, and the somatic genome and phenotypic changes characteristic of prostate cancer cells. We also present the implications of these changes for prostate cancer diagnosis, detection, prevention, and treatment. *J. Cell. Biochem.* 91: 459–477, 2004. © 2003 Wiley-Liss, Inc.

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MECHANISMS OF INFLAMMATION INDUCED CARCINOGENESIS

Chronic or recurrent inflammation is responsible for the development of many human

cancers, including those affecting the liver, esophagus, stomach, large intestine, and urinary bladder [Coussens and Werb, 2002]. Inflammation might influence the pathogenesis of cancers by (i) inflicting cell and genome damage, (ii) triggering restorative cell proliferation to replace damaged cells, (iii) elaborating a portfolio of cytokines that promote cell replication, angiogenesis and tissue repair [Coussens and Werb, 2002].

Oxidative damage to DNA and other cellular components accompanying chronic or recurrent inflammation may connect prostate inflammation with prostate cancer. In response to infections, inflammatory cells produce a variety of toxic compounds designed to eradicate microorganisms. These include superoxide, hydrogen peroxide, singlet oxygen, as well as nitric oxide that can react further to form the highly

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*Correspondence to: Angelo M. De Marzo, Room 153, Bunting-Blaustein Cancer Research Building, Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, 1650 Orleans Street, Baltimore, MD 21231-1000.

E-mail: ademarz@jhmi.edu

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reactive peroxyxynitrite. Some of these reactive oxygen and nitrogen species can directly interact with DNA in the host bystander cells, or react with other cellular components such as lipid, initiating a free radical chain reaction. If the damage is severe, these compounds can kill host bystander cells as well as pathogens, and can produce DNA damage and mutations among host cell survivors [Xia and Zweier, 1997; Eiserich et al., 1998]. As a consequence of an acquired defect in defenses against oxidant and electrophilic carcinogens associated with *GSTP1* CpG island hypermethylation (see below), prostate cells may acquire a heightened susceptibility to oxidative genome damage in an inflammatory milieu, leading to neoplastic transformation and cancer progression. Other support for the concept that prostate cancer can result from excess oxidants and electrophiles comes from epidemiological studies suggesting that decreased prostate cancer risk is associated with intake of various anti-oxidants and non-steroidal anti-inflammatory drugs [Clark et al., 1996, 1998; Heinonen et al., 1998; Norrish et al., 1998; Gann et al., 1999; Nelson and Harris, 2000; Roberts et al., 2002]. In further support of a critical role for oxidative genome damage during the pathogenesis of prostate cancer, variant polymorphic alleles at *OGG1*, the gene encoding a DNA glycosylase/AP lyase that repairs the oxidized base 8-oxo-G in DNA, are associated with increased prostate cancer risk [Xu et al., 2002b].

PROSTATE INFLAMMATION AND THE PATHOGENESIS OF PROSTATE CANCER

At least three major disease processes are extremely common in the prostate—prostatitis, benign prostatic hyperplasia (BPH), and adenocarcinoma. Why do three apparently distinct types of lesions occur so commonly in the same organ, and might these common processes be linked? Despite the fact that prostate inflammation (histological prostatitis) and prostate cancer are often found in the same patient, associations between inflammation and prostate cancer have not been clearly shown. This may be due in part to the following difficulties in performing association studies of prostate cancer and prostatitis: (i) most prostate inflammation does not seem to cause symptoms [True et al., 1999], (ii) the incidence of asymptomatic histologic prostatitis in non-selected population

based studies is difficult to ascertain [Giovannucci, 2001], (iii) the clinical diagnosis of chronic prostatitis itself can be challenging and is often subjective [Roberts et al., 1998]. Although large-scale prospective epidemiological studies are lacking [Giovannucci, 2001], a recent review of the available epidemiological literature by Dennis et al. [2002] indicates that there may be a small increase in the relative risk of the development of prostate cancer in men with a history of clinical prostatitis. Given the high prevalence of prostate cancer, however, even a small increase in relative risk can result in a large number of additional cases.

In terms of the prevalence of clinical prostatitis, a survey of clinical data in Olmstead county Minnesota reported that symptomatic prostatitis occurred in approximately 9% of men between 40 and 79 years of age, with half of these men suffering more than one episode, and it was estimated that 1 in 11 men will be diagnosed with some form of prostatitis by age 79 years [Roberts et al., 1998]. In terms of histological prostatitis, inflammatory infiltrates of varying intensity and character are readily apparent in most radical prostatectomy [Gerstenbluth et al., 2002] and transurethral resection specimens [Nickel et al., 1999], and prostate needle biopsies [Schatteman et al., 2000].

The current NIH consensus classification system of prostatitis divides the cases into four categories—3 that are associated with genitourinary symptoms and 1 that is not [Krieger et al., 1999]. Category I, or *acute bacterial prostatitis*, is usually caused by *Escherichia coli* or other gram-negative bacteria or enterococcus. Acute bacterial prostatitis is infrequent and consists of an acutely swollen and tender prostate with acute inflammatory cells in expressed prostate fluid. There is usually an associated urinary tract infection, and, at times systemic symptoms of infection. Acute prostatitis is usually self-limited after treatment with antibiotics. Category II, or *chronic bacterial prostatitis*, is quite rare, and consists of repeated bouts of lower urinary tract infection where the source of infection can be localized to the prostate. This form is also usually treated with antibiotics, often with multiple courses over time. Category III is the most common form, accounting for approximately 90% of clinical prostatitis syndromes, and is referred to as *chronic prostatitis/chronic pelvic pain syndrome*. The cardinal feature of this entity is pain, either in

the perineum, external genitalia, or other sites in the pelvis. There is also frequently pain during or after ejaculation. The symptoms must be of at least 3 months in duration to be considered chronic. This form is subdivided into those cases where leukocytes are identifiable on expressed prostatic fluids, post-prostate massage urine, or semen (category IIIA— inflammatory) and those that do not contain leukocytes in these fluids (category IIIB— chronic prostatitis/chronic pelvic pain syndrome). Category IV, or *asymptomatic inflammatory prostatitis*, represents the presence of prostate inflammation in histological tissue sections from men with no history of urinary symptoms.

In addition to the putative increased risk of prostate cancer with a history of symptomatic prostatitis, an increased prostate cancer risk has been associated in some studies [e.g., Hayes et al., 2000] with sexually transmitted infections [reviewed in Strickler and Goedert, 2001; Dennis and Dawson, 2002], independent of the specific pathogen, supporting the concept that inflammation itself might facilitate prostatic carcinogenesis, or, that the associative causative organism(s) has not been identified. Of significance in this regard, two of the candidate hereditary prostate cancer susceptibility genes identified thus far, *RNASEL* and *MSR1*, encode proteins that function in the host responses to a variety of infectious agents [Zhou et al., 1997; Platt and Gordon, 2001; Carpten et al., 2002; Xu et al., 2002a].

Relation of Prostate Cancer, Benign Prostatic Hyperplasia, and Inflammation

The fact that most prostate cancer and most inflammatory infiltrates are both present in the peripheral zone [McNeal, 1997] is consistent with a link between inflammation and prostate cancer. What about the transition zone, the site of development of BPH? Is there a link between BPH and prostate cancer? Is there a link between inflammation and BPH?

Approximately 25% of prostate adenocarcinomas appear to arise in the transition zone. Thus, while the peripheral zone is the site of origin of prostate cancer in the majority of the cases, when compared to other organs that seem to be protected from cancer development (such as the seminal vesicles), prostate transition zone cancer is actually quite common. In terms of epidemiological data, the relation between

BPH and prostate cancer has been reviewed recently, where it was concluded that none of the epidemiologic studies published to date have provided clear evidence suggesting an etiologic role for BPH in the development of prostate cancer [Guess, 2001]. However, the author also indicated that most of the studies had at least some major bias and that it might be perhaps more important to examine the biology and pathology of any potential connection [Guess, 2001].

In terms of pathobiology, Bostwick et al. [1992] summarized the facts that BPH and prostate cancer tend to occur in the same patient, share similar hormonal requirements for growth, and can occur in proximity. Pathologically, it appears that transition zone cancers do indeed appear to arise in the setting of nodules of BPH [Bostwick et al., 1992; Leav et al., 2003, and references therein], and occasionally from adenosis [Bostwick and Qian, 1995; Grignon and Sakr, 1996], which is also referred to as atypical adenomatous hyperplasia. While these transition zone tumors are often of somewhat lower Gleason score, they are quite common in radical prostatectomy and TURP specimens [Leav et al., 2003]. Often in radical prostatectomies transition zone cancers are found incidentally after the diagnosis of prostate cancer in the peripheral zone, which is much more widely sampled at needle biopsy. Whether there are an equal number of transition zone cancers in men without significant nodular hyperplasia is currently not clear. Thus, although there is no strong evidence linking the two, the relation between BPH and prostate cancer remains an open issue. In addition, it is possible that BPH and prostate cancer are both caused by similar exposures, such that they commonly occur together but are not directly linked in a precursor-progeny pathway.

What is the relation between transition zone cancer and inflammation? While the relation between inflammation and transition zone cancer is unknown, it is known that BPH tissue contains a variable amount of chronic and often acute inflammation in virtually 100% of specimens [Nickel et al., 1999]. It has been reported that levels of serum PSA in BPH patients correlates with the amount of tissue injury associated with inflammation [Hasui et al., 1994; Irani et al., 1997; Schatteman et al., 2000; Yaman et al., 2003], and some have submitted that the pathogenesis [Gleason et al., 1993],

and/or clinical features [Nickel, 1994] of BPH may be related to prostate inflammation. Still unclear, however, is whether inflammation comes prior to BPH nodule formation or whether it is a response to the altered tissue architecture resulting from the nodules. While no firm conclusions can be drawn presently, the pathological literature is consistent with a model whereby inflammation, due to infection or otherwise, is related to the development or progression of BPH, and in some circumstances BPH is related to prostate cancer. Although, more study of this issue is required, it is plausible that inflammation may be related to transition zone cancer.

Proliferative Inflammatory Atrophy

Pathologists have long recognized focal areas of epithelial atrophy in the prostate [Rich, 1934; Moore, 1936; Franks, 1954]. These focal areas of epithelial atrophy, distinct from the diffuse atrophy seen after androgen deprivation, usually appear in the periphery of the prostate, where prostate cancers typically arise [Rich, 1934; McNeal, 1988]. Many of these areas of epithelial atrophy are associated with acute or chronic inflammation [Franks, 1954; McNeal, 1997; Ruska et al., 1998; De Marzo et al., 1999], contain proliferative epithelial cells [Liavag, 1968; Feneley et al., 1996; Ruska et al., 1998; De Marzo et al., 1999; Shah et al., 2001], and may show morphological transitions in continuity with high grade prostatic intraepithelial neoplasia (PIN) lesions [De Marzo et al., 1999; Putzi and De Marzo, 2000], putative prostate cancer precursors [McNeal and Bostwick, 1986; Bostwick, 1996]. At times these atrophic lesions may show evidence of direct transitions to minute carcinoma lesions, with little or no recognizable PIN component [Franks, 1954; Liavag, 1968; Montironi et al., 2002; Nakayama et al., 2003]. Focal atrophy of the prostate exists as a spectrum of morphologies and areas containing it in the prostate can be quite extensive. Most of these morphological patterns fit into the categories of simple atrophy, or post-atrophic hyperplasia, as described by Ruska et al. [1998]. To highlight the common association with inflammation and the unexpectedly high proliferation index, we have put forth the term proliferative inflammatory atrophy (PIA) to encompass these lesions [De Marzo et al., 1999]. In terms of the requirement for inflammatory cells in PIA, the majority of all focal atrophy lesions

contain at least some increase in chronic and/or acute inflammation. Also, since the amount of inflammation from field to field within a given atrophy lesion can be highly variable we have recently suggested that to refer to a lesion as PIA does not require easily recognizable inflammation—thus, most forms of focal glandular atrophy can be considered PIA [Van Leenders et al., 2003]. A working group to formalize terminology of the various atrophic lesions in the prostate is currently being formed, and a preliminary meeting with a group of pathologists and other investigators was held at the NIH campus in February of 2003.

In support of PIA as a prostate cancer precursor, prostate inflammation, accompanied by focal epithelial atrophy, has been proposed to contribute to prostate cancer development in rats [Reznik et al., 1981; Wilson et al., 1990]. Further support comes from the fact that PIA shares several molecular alterations found in both PIN and carcinoma. For example, chromosome 8 gain, detected by fluorescence in situ hybridization (FISH) with a chromosome 8 centromere probe, was found in human PIA, PIN, and prostate cancer [Macoska et al., 2000; Shah et al., 2001]. Others have recently documented rare p53 mutations in one variant of PIA, referred to as post-atrophic hyperplasia [Tsujiimoto et al., 2002] and, our group has recently shown that approximately 6% of PIA lesions show evidence of somatic methylation of the *GSPT1* gene promoter [Nakayama et al., 2003a] (see description of *GSPT1* promoter methylation below). While the cause of focal atrophy lesions is not known, they may arise either as a consequence of epithelial damage, e.g., from infection, ischemia [Billis, 1998], or toxin exposure (including dietary oxidants/electrophiles or endogenous chemicals such as estrogens, etc.), followed by epithelial regeneration and associated secondary inflammation, or as a direct consequence of inflammatory oxidant damage to the epithelium [De Marzo et al., 1999]. The process of aging itself has been suggested to contribute to some morphological variants of prostate atrophy [McNeal, 1984]. Regardless of the etiology of PIA, the epithelial cells in these lesions exhibit many molecular signs of stress, expressing high levels of *GSPT1*, *GSTA1*, and cyclo-oxygenase 2 (*COX-2*) [De Marzo et al., 1999; Putzi and De Marzo, 2000; Parsons et al., 2001b; Zha et al., 2001]. There is also mounting evidence that many of the

atrophic luminal cells in PIA represent a form of intermediate epithelial cell [Van Leenders et al., 2003]—cells with features intermediate between basal and luminal secretory cells. Intermediate epithelial cells have been postulated to be the targets of neoplastic transformation in the prostate [Verhagen et al., 1992; De Marzo et al., 1998a,b; van Leenders et al., 2000].

It should be noted that not all authors have found associations between prostate atrophy and prostate cancer [McNeal, 1969; Billis, 1998; Anton et al., 1999; Billis and Magna, 2003], and that in our own studies not all high grade PIN or small carcinoma lesions are associated with atrophy [Putzi and De Marzo, 2000]. Most studies of the connection between atrophy and cancer have focused on peripheral zone cancer nearly exclusively. Thus, additional studies are required to more fully understand the relation between focal atrophy and cancer in the prostate. Our current concept is that PIA is a common proliferative response to environmental stimuli in aging men and that some high grade PIN and carcinoma lesions arise as a consequence of genome damage in PIA, while others do not. A corollary to this is that while only a subset of atrophy lesions may be pre-neoplastic, the fact that atrophic areas can be so widespread and multi-focal in the prostate is consistent with the hypothesis that many prostate cancers can indeed arise from PIA.

SOMATIC GENOME ALTERATIONS ACCOMPANYING PROSTATIC CARCINOGENESIS

Similar to other types of epithelial cancer, prostate cancers contain many somatic genomic alterations, including point mutations, deletions, amplifications, chromosomal rearrangements, and changes in DNA methylation [Isaacs et al., 1994; Bookstein, 2001; Chung et al., 2001; Gao and Isaacs, 2002; Meng and Dahiya, 2002; DeMarzo et al., 2003]. However, unlike some carcinomas such as those of the colon/rectum [Kinzler and Vogelstein, 1997] and pancreas [Jaffee et al., 2002], where specific oncogenes such as *k-ras* or tumor suppressor genes such as *p53* are mutated at a very high frequency, gene mutations reported thus far in prostate cancer appear quite heterogeneous, from case to case, or even from lesion to lesion in a single case [Isaacs et al., 1994; Mirchandani et al., 1995; Qian et al., 1995; Ruijter et al., 1999; Bookstein,

2001; Chung et al., 2001; Gao and Isaacs, 2002; Meng and Dahiya, 2002]. In addition, genetic alterations appear to accumulate with prostate cancer progression. Small prostate cancers are present in nearly 30% of men between 30–40 years of age in the U.S., though most men are diagnosed with prostate cancer at 50–70 years of age [Sakr et al., 1994]. The progression of these small prostate cancers to larger life-threatening cancers, and the accumulation of somatic genome abnormalities, appears sensitive to environmental factors and lifestyle. Prostate cancer incidence and mortality are very high in the U.S. and Western Europe, while lower prostate cancer risks and death rates are characteristic of Asia [Miller, 1999; Hsing et al., 2000]. In support of an effect of environment and lifestyle on prostate cancer development, Asian immigrants to North America tend to acquire higher prostate cancer risks within one generation [Haenszel and Kurihara, 1968; Shimizu et al., 1991; Whittemore et al., 1995]. Whether the appearance of somatic genome alterations in prostate cancer cells is the result of chronic or recurrent exposure to genome-damaging stresses, defective protection against genome damage, or a combination of both processes, has not been definitively shown.

GSTP1

Hypermethylation of CpG island sequences encompassing the promoter region of *GSTP1*, encoding the π -class glutathione *S*-transferase (GST), is an exceedingly common somatic genome change found in prostate cancer [Lee et al., 1994; Millar et al., 1999; Lin et al., 2001; Nelson et al., 2001b]. Immunohistochemistry has demonstrated that *GSTP1* protein is normally expressed in basal epithelial cells in the prostate, but is absent in most luminal columnar secretory epithelial cells. In PIA lesions, strong anti-*GSTP1* staining is seen in many of the atrophic luminal epithelial cells, [De Marzo et al., 1999] consistent with the induction of expression in response to environmental stress. The luminal cells in PIA are not simply basal cells, as shown by their lack of expression of p63 [Parsons et al., 2001a]. In prostate cancer cells, somatic hypermethylation of *GSTP1* CpG island sequences represses *GSTP1* transcription [Lin et al., 2001]. Absence of *GSTP1* expression and *GSTP1* CpG island hypermethylation are also common in high-grade PIN lesions [Brooks et al., 1998].

GSTP1 is not a classical tumor suppressor gene [Lin et al., 2001]. Rather, *GSTP1* more likely plays a “caretaker” role, protecting prostate epithelial cells against genome damage mediated by carcinogens [Kinzler and Vogelstein, 1997]. For example, mice with both *GSTP1* alleles disrupted by gene targeting exhibit increased skin tumor formation after topical exposure to the skin carcinogen 7,12-dimethylbenz [a] anthracene (DMBA) [Henderson et al., 1998]. One prostate carcinogen that may be detoxified by *GSTP1* is the dietary heterocyclic amine, 2-amino-1-methyl-6-phenylimidazo [4,5-*b*]pyridine (PhIP), which forms when meats are cooked at high temperatures or “charbroiled” [Lijinsky and Shubik, 1964; Gross et al., 1993; Morgenthaler and Holzhauser, 1995; Knize et al., 1997]. Dietary PhIP intake causes prostate cancer in rats [Shirai et al., 1997; Stuart et al., 2000]. In humans, a study examining the association between PhIP and other heterocyclic amine intake and prostate cancer showed a modest, albeit inconsistent increased relative risk of prostate cancer with increasing consumption [Norrish et al., 1999], although there are a large number of studies showing an association between an increased relative risk of overall prostate cancer and the levels of consumption of red meat [reviewed in Kolonel, 2001]. In the most recent analysis from the Health Professionals Follow-Up Study, consumption of red meats was not associated with an increased risk of prostate cancer overall, but was associated with increased risk of metastatic prostate cancer [Michaud et al., 2001]. *GSTP1* can protect prostate cells against PhIP damage: for LNCaP prostate cancer cells, which do not express *GSTP1*, exposure to metabolically activated PhIP results in the appearance of pro-mutagenic PhIP–DNA adducts. Replacement of the *GSTP1* gene by stable transfection prevented PhIP–DNA damage [Nelson et al., 2001a]. *GSTP1* may also protect prostate cells against damage inflicted directly by oxidants, such as those produced by protracted low dose ionizing radiation exposure (DeWeese et al., unpublished observations).

AR

Androgenic hormones and the androgen receptor (AR) both play critical roles in normal prostate development and function, and in most prostate diseases, including prostate cancer. For example, transgenic mice engineered to

express high levels of the androgen receptor in the prostate tend to develop PIN [Stanbrough et al., 2001]. Many somatic alterations of *AR*, encoding the androgen receptor, have been described in human prostate cancers, particularly “androgen-independent” prostate cancers appearing after treatment by androgen suppression and/or with anti-androgens [Veldscholte et al., 1990; Newmark et al., 1992; Suzuki et al., 1993, 1996; Gaddipati et al., 1994; Schoenberg et al., 1994; Taplin et al., 1995, 1999; Visakorpi et al., 1995; Evans et al., 1996; Tilley et al., 1996; Koivisto et al., 1997; Marcelli et al., 2000; Haapala et al., 2001]. “Androgen-independent” prostate cancers usually continue to express the androgen receptor, maintaining androgen-receptor dependent signaling (i) in response to the reduced levels of circulating androgens, such as with *AR* amplification accompanied by androgen receptor over-expression, (ii) in response to non-androgens or anti-androgens as agonist ligands, such as with *AR* mutations accompanied by altered androgen receptor ligand specificity, or (iii) via ligand-independent activation of the androgen receptor, such as may occur under the influence of other intracellular signal transduction pathways [Veldscholte et al., 1990; van der Kwast et al., 1991; Culig et al., 1993; Nazareth and Weigel, 1996; Koivisto et al., 1997; Tan et al., 1997; Hobisch et al., 1998; Craft et al., 1999; Amler et al., 2000; Sadar and Gleave, 2000; Feldman and Feldman, 2001; Mousses et al., 2001; Zegarra-Moro et al., 2002].

NKX3.1

NKX3.1, located at 8p21, encodes a prostate-specific homeobox gene essential for normal prostate development [Bieberich et al., 1996; He et al., 1997; Sciavolino et al., 1997; Prescott et al., 1998]. In mice, targeted disruption of *Nkx3.1* leads to prostatic epithelial hyperplasia and dysplasia [Bhatia-Gaur et al., 1999; Abdulkadir et al., 2002]. In men, although loss of 8p21 DNA sequences has been reported in as many as 63% of PIN lesions and in more than 90% of prostate cancers, no *NKX3.1* mutations have been detected, leading to controversy over whether *NKX3.1* is the gene target of somatic alteration at 8p21 [Emmert-Buck et al., 1995; He et al., 1997; Voeller et al., 1997; Ornstein et al., 2001]. Nonetheless, loss of *NKX3.1* expression has been reported in as many as 20% of PIN lesions, 6% of low stage prostate cancers,

22% of high stage prostate cancers, 34% of androgen-independent prostate cancers, and 78% of prostate cancer metastases [Bowen et al., 2000]. The relationship between somatic *NKX3.1* alterations and reduction in *NKX3.1* expression during prostate cancer development has not been determined.

PTEN

PTEN, located at 10q, another site of frequent allelic loss in prostate cancer, encodes a phosphatase active against both proteins and lipid substrates [Li et al., 1997; Myers et al., 1997, 1998; Steck et al., 1997; Teng et al., 1997]. *PTEN* has been proposed to function as a general tumor suppressor by inhibiting the phosphatidylinositol 3'-kinase/protein kinase B (PI3K/Akt) signaling pathway, thought to be essential for cell cycle progression and/or cell survival in many cell types [Li et al., 1997; Furnari et al., 1998; Ramaswamy et al., 1999; Sun et al., 1999]. Like mice carrying disrupted *Nkx3.1* alleles, mice carrying disrupted *Pten* alleles manifest prostatic hyperplasia and dysplasia, and the progeny of breeding crosses between *Pten* \pm mice and *Nkx3.1* \pm mice develop PIN [Bhatia-Gaur et al., 1999; Podsypanina et al., 1999; Di Cristofano et al., 2001; Kim et al., 2002], as well as invasive carcinoma and lymph node metastases [Abate-Shen et al., 2003]. *PTEN*, which is typically expressed by normal epithelial cells, is often expressed at a reduced level in human prostate cancer cells [McMenamin et al., 1999]. Many somatic *PTEN* alterations have been reported for prostate cancers, including homozygous deletions, loss of heterozygosity, mutations, and suspected CpG island hypermethylation [Cairns et al., 1997; Li et al., 1997; Myers et al., 1997, 1998; Steck et al., 1997; Teng et al., 1997; Gray et al., 1998; Suzuki et al., 1998; Wang et al., 1998; Vivanco and Sawyers, 2002]. Associations between somatic *PTEN* alterations and aberrant *PTEN* function in prostate cancer cells have been difficult to establish. Often, losses of 10q sequences near *PTEN* do not appear to be accompanied by somatic mutations of the remaining *PTEN* allele. Furthermore, although somatic *PTEN* alterations appear more common in metastatic than in primary prostate cancer lesions, a marked heterogeneity in *PTEN* defects in different metastatic sites from the same patient has been reported [Suzuki et al., 1998]. Perhaps, as is evident in mouse models featuring disrupted *Nkx3.1*

and *Pten* genes, haploinsufficiency for *PTEN* and/or *NKX3.1* may be sufficient for a neoplastic phenotype [Bhatia-Gaur et al., 1999; Podsypanina et al., 1999; Di Cristofano et al., 2001; Kim et al., 2002].

CBKN1B

p27, a cyclin-dependent kinase inhibitor encoded by *CDKN1B*, may also be a somatic gene target for alteration during prostatic carcinogenesis. Targeted disruption of *Cdkn1b* in mice results in prostatic hyperplasia, while mice carrying disrupted *Pten* and *Cdkn1b* alleles develop localized prostate cancers [Di Cristofano et al., 2001]. Reduced p27 expression appears characteristic of human prostate cancer cells, particularly in prostate cancer cases with a poor prognosis [Guo et al., 1997; Cheville et al., 1998; Cordon-Cardo et al., 1998; Yang et al., 1998; De Marzo et al., 1998a]. Somatic loss of DNA sequences at 12p12-13, near *CDKN1B*, have been reported for 23% of localized prostate cancers, 30% of prostate cancer lymph node metastases, and 47% of prostate cancer distant metastases [Kibel et al., 2000]. The mechanism(s) by which somatic *CDKN1B* alterations leads to reduced p27 expression have not been elucidated. Provocatively, p27 may be a target for repression by the PI3K/Akt signaling pathway [Li and Sun, 1998; Sun et al., 1999; Graff et al., 2000; Gottschalk et al., 2001]. Thus, loss of *PTEN* function, accompanied by increased PI3K/Akt signaling, might result in decreases in *CDKN1B* mRNA and in p27 protein half-life [Nakamura et al., 2000]. Decreased p27 expression has also been documented in high grade PIN [De Marzo et al., 1998a; Fernandez et al., 1999] and in PIA lesions [De Marzo et al., 1998a; Van Leenders et al., 2003].

Telomeres, Telomere Shortening, and Telomerase

The karyotype of most human cancers is abnormal. Many types of cancer, including prostate cancer, show chromosomal instability reflected by aberrations in both number and structure of chromosomes. The exceptions to this in solid tumors are cancers with microsatellite instability, which are genetically unstable at the single nucleotide level but contain mostly diploid karyotypes. Chromosomal instability appears to be an important molecular mechanism driving malignant transformation in many human

epithelial tissues [Cahill et al., 1999], yet the molecular mechanisms responsible for chromosome destabilization during carcinogenesis are largely unknown. One route to chromosomal instability is through defective telomeres [Counter et al., 1992; Hackett and Greider, 2002; Feldser et al., 2003]. Telomeres, which consist of multiple repeats of a 6 base pair unit (TTAGGG), complexed with several different binding proteins, protect chromosome ends from fusing with other chromosome ends or other chromosomes containing double strand breaks [McClintock, 1941]. However, in the absence of compensatory mechanisms, telomeric DNA is subject to loss due to cell division [Harley et al., 1990; Levy et al., 1992] and possibly oxidative damage [von Zglinicki et al., 2000]. Critical telomere shortening leads to chromosomal instability that, in mouse models, causes an increased cancer incidence that is likely a result of chromosome fusions, subsequent breakage, and rearrangement [Blasco et al., 1997; Artandi et al., 2000]. Intriguingly, telomeres within human carcinomas are often found to be abnormally reduced in length [de Lange, 1995], but the timing of this phenomenon has been unclear. In human prostate cancer, the telomeres from prostate cancer tissue were consistently shorter than those from cells in either the adjacent normal or BPH tissues [Sommerfeld et al., 1996]. Others have also reported telomere shortening in prostate cancer [Donaldson et al., 1999].

Most carcinomas arise from pre-invasive intraepithelial precursor lesions, referred to as intraepithelial neoplasias (IEN) [O'Shaughnessy et al., 2002]. These lesions show morphological features and molecular alterations characteristic of malignant neoplasia, including evidence of genetic instability [Shih et al., 2001] but occur within preexisting epithelia and are confined within the basement membrane. If genetic instability helps to drive cancer formation, and telomeres shortening is a major mechanism leading to genetic instability, then telomere shortening should be present at the intraepithelial phase of carcinoma. Recently we employed an in situ telomere FISH technique TEL-FISH and reported that telomere shortening is evident in the majority of high-grade prostatic intraepithelial neoplasia (PIN) lesions [Meeker et al., 2002], which are thought to be cancer precursor lesions of the prostate. Thus, telomere shortening is a prevalent biomarker in human prostate, occurring early in the process of

prostate carcinogenesis. Interestingly, the telomere shortening found in high grade PIN was restricted to the luminal cells and was not present in the underlying basal cells. This finding strongly suggests that basal cells are not the direct precursor cell to high grade PIN, but support the above mentioned concept that cells with an intermediate luminal cell phenotype are the likely direct target cell of transformation in the prostate. Vukovic et al., recently reported similar findings of reduced telomere length in high grade PIN and prostate cancer [Vukovic et al., 2003].

Hepsin, AMACR, and EZH2

Alterations in gene expression accompanying the development of prostate cancer have been surveyed using transcriptome profiling technologies [Huang et al., 1999; Walker et al., 1999; Nelson et al., 2000; Xu et al., 2000; Dhanasekaran et al., 2001; Luo et al., 2001, 2002; Magee et al., 2001; Stamey et al., 2001; Waghray et al., 2001; Welsh et al., 2001]. Among the many genes exhibiting over- or under-expression in localized prostate cancers, the products of at least two genes appear consistently increased. *Hepsin*, located at 19q11-13.2, encodes a transmembrane serine protease, normally expressed at high levels in the liver and other tissues [Tsuji et al., 1991]. The contribution of hepsin to the prostate cancer phenotype has not been discerned. Anti-sense oligonucleotides targeting *Hepsin* mRNA have been reported to retard the growth of hepatoma cells, but *Hepsin*^{-/-} mice develop normally, exhibit normal liver regeneration, and have no striking phenotype [Torres-Rosado et al., 1993; Wu et al., 1998; Yu et al., 2000]. α -Methylacyl-CoA racemase, a mitochondrial and peroxisomal enzyme that acts on pristanoyl-CoA and C27-bile acyl-CoA substrates to catalyze the conversion of *R*- to *S*-stereoisomers in order to permit metabolism by β -oxidation [Schmitz et al., 1995], has been reported to be over-expressed in almost all prostate cancers [Xu et al., 2000; Dhanasekaran et al., 2001; Luo et al., 2001, 2002]. Germline *AMACR* mutations have been reported to lead to adult-onset neuropathy [Ferdinandusse et al., 2000]. Immunohistochemistry studies have revealed that α -methylacyl-CoA racemase is occasionally present in normal prostate cells, increased in prostatic intraepithelial neoplasia cells, and further elevated in prostate cancer cells [Jiang et al., 2001, 2002; Beach et al., 2002;

Luo et al., 2002; Rubin et al., 2002; Yang et al., 2002; Leav et al., 2003; Magi-Galluzzi et al., 2003; Zhou et al., 2003a]. Another gene product shown to be increased at the mRNA level in primary and hormone refractory metastatic prostate cancer using gene expression arrays is the polycomb group protein enhancer of zeste homolog 2 (EZH2), which has been postulated to be involved in the progression of prostate cancer [Varambally et al., 2002].

IMPLICATIONS FOR PROSTATE CANCER DIAGNOSIS, DETECTION, PREVENTION, AND TREATMENT

AMACR, p63, and the Diagnosis of Prostate Cancer

It is estimated that approximately 1,000,000 prostate needle biopsies are performed per year in the U.S., and approximately 20% are positive for cancer. While there is no standard for the number of cores taken, in many institutions urologists are submitting 12 or more cores per patient, which is up from 6 several years ago. Thus, between 6 and 12 million individual new needle biopsy cores are examined microscopically by pathologists each year in the U.S. While at times the diagnosis of prostate cancer on needle biopsy can be quite straightforward, many cases present diagnostic challenges. For example, there are many benign mimics of prostate cancer that can be misdiagnosed as prostate cancer [Epstein, 1995; Epstein and Potter, 2001; DeMarzo et al., 2003]. These include lesions such as atrophy adenosis (atypical adenomatous hyperplasia), PIN, nephrogenic adenoma granulomatous prostatitis, and radiation change in benign glands. It has been clear for many years that prostate basal cells, which are uniformly present in normal appearing prostate acini and ducts, and in the vast majority of benign mimics of prostate cancer, are absent in prostate cancer [Brawer et al., 1985]. Thus, ancillary tools such as immunohistochemistry against "basal cell specific cytokeratins"¹ are often employed in difficult cases to determine if a particular suspicious lesion

contains basal cells [Hedrick and Epstein, 1989]. More recently it has been shown that the product of the *p63* gene is expressed in basal cell nuclei in the prostate, but not in prostate luminal cells nor in the vast majority of prostate cancers [Signoretti et al., 2000; Parsons et al., 2001a]. Since this marker may be more robust in terms of surviving poor fixation or various types of tissue processing [Weinstein et al., 2002], many pathologists have begun to employ p63 staining in clinical practice to further determine whether basal cells may be present in a suspicious lesion [Shah et al., 2002]. To increase the chances of finding basal cells, Zhou et al. [2003b] have recently suggested using a cocktail of antibodies against basal cell cytokeratins and p63.

As indicated above, AMACR has been found by a large number of different investigators to be overexpressed in prostate cancer cells. Since negative staining for basal cell markers by itself is not diagnostic of prostate cancer, positive staining for AMACR may increase the level of confidence in establishing a definitive malignant diagnosis in a lesion deemed highly suspicious by standard H&E staining [Jiang et al., 2001, 2002; Beach et al., 2002; Magi-Galluzzi et al., 2003; Zhou et al., 2003a]. Thus, many pathologists have begun to employ this marker. At our institution we routinely order the p63, 34BE12 (also referred to as keratin 903), and AMACR on atypical prostate needle biopsies where the suspicion of cancer is high but the findings on H&E section are insufficient to render a clearly malignant diagnosis. In the research setting, we have also employed double labeling against p63 (nuclear staining positive in basal cells) and racemase (cytoplasmic-only staining) in order to delineate both markers on an individual tissue sections [Luo et al., 2002], although this double labeling can be somewhat problematic on needle biopsies due to background cytoplasmic staining for p63.

As usual with any ancillary test, there are pitfalls in the use of AMACR in diagnostic pathology, since certain histological subtypes of prostatic adenocarcinoma tend to be weak or negative for this marker [Zhou et al., 2003a], and, benign glands and high grade PIN may be positive at times. Since there are so many diagnostic pitfalls in prostate needle biopsies, the importance of obtaining second opinions on prostate biopsy material has been emphasized [Epstein et al., 1996].

¹Often staining for basal cells is performed with the monoclonal antibody 34BE12, recognizing a range of high molecular weight cytokeratins including keratin 5 and 14. These keratins are highly expressed in basal cells. Other antibodies against keratin 5 have also been employed.

GSTP1 CpG Island Hypermethylation and the Detection of Prostate Cancer

Abnormal genes and gene products appearing in prostate cancer cells offer great promise as disease biomarkers. For example, *GSTP1* CpG island hypermethylation, detected in prostate tissue, blood, urine, or prostate fluid, may be a molecular biomarker useful for prostate cancer detection and staging. Although *GSTP1* CpG island hypermethylation has been found in DNA from more than approximately 90% of prostate cancers, approximately 70% of liver cancers, and approximately 30% of breast cancers, this genome alteration has not been detected in DNA from any normal tissues [Lee et al., 1994; Esteller et al., 1998; Tchou et al., 2000; Lin et al., 2001; Nakayama et al., 2003]. *GSTP1* CpG island hypermethylation has also been detected in 70% of PIN lesions [Brooks et al., 1998; Nakayama et al., 2003a]. For a comprehensive review of *GSTP1* methylation as a biomarker in prostate cancer, see the accompanying article by Nakayama et al. [2003b].

Carcinogen Detoxification, Inflammation, and Prostate Cancer Prevention

Insights into the molecular pathogenesis of prostate cancer may provide opportunities for the discovery and development of new agents for prostate cancer prevention. Loss of *GSTP1* "caretaker" activity during prostate carcinogenesis emphasizes the critical role of carcinogen metabolism in protecting prostate cells against neoplastic transformation, and suggests that therapeutic compensation for inadequate *GSTP1* "caretaker" function may help prevent prostate cancer. The "oxidation tolerance" phenotype associated with loss of *GSTP1* "caretaker" function in LNCaP prostate cancer cells may provide a mechanistic rationale for buttressing defenses against oxidative genome damage via anti-oxidant supplementation to prevent or delay prostate carcinogenesis. In addition, augmentation of carcinogen-detoxification capacity, using a variety of such chemoprotective compounds, including isothiocyanates, 1,2-dithiole-3-thiones, terpenoids, etc., is known to prevent a range of different cancers in different animal models by triggering the expression of many different carcinogen-detoxification enzymes [Kensler, 1997; Ramos-Gomez et al., 2001]. Oltipraz, an inducer of carcinogen-detoxification enzymes in liver tis-

ues, has been shown to reduce aflatoxin B₁ damage when administered to a human clinical study cohort at high risk for aflatoxin exposure and liver cancer development in China [Jacobson et al., 1997; Kensler et al., 1998; Wang et al., 1999]. Sulforaphane, an isothiocyanate present in high amounts in cruciferous vegetables, is also a potent inducer of carcinogen-detoxification enzymes [Zhang et al., 1992, 1994]. Diets rich in carcinogen-inducers like sulforaphane have been associated with decreased cancer risks [Cohen et al., 2000]. Such carcinogen-detoxification enzyme inducers need to be developed and tested in prostate cancer prevention clinical trials.

The recognition that prostate inflammation may contribute to the earliest steps in prostate carcinogenesis also has profound implications for the prevention of prostate cancer. Animal model studies suggest that non-steroidal anti-inflammatory drugs might attenuate both prostate cancer incidence and prostate cancer progression [Wechter et al., 2000]. In addition, several epidemiology studies have hinted at a modest protective effect of non-steroidal anti-inflammatory drug intake on either prostate cancer incidence, or on prostate cancer progression [Norrish et al., 1998; Nelson and Harris, 2000; Habel et al., 2002; Leitzmann et al., 2002; Roberts et al., 2002]. One target of these drugs, cyclo-oxygenase-2 (COX-2), may be selectively expressed in PIA lesions in the prostate [Zha et al., 2001]. A randomized clinical trial involving the administration of celecoxib, a selective COX-2 inhibitor, or placebo to men with prostate cancer who undergo radical prostatectomy, has been initiated at the Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins. The effects of COX-2 inhibition on oxidative genome damage on PIA and on other tissue markers will be ascertained. In the future, as the process of inflammation in the prostate, and the pathogenesis of PIA becomes better defined more specific targets will be identified, creating new opportunities for the discovery and development of selective inhibitors of pathways mediating prostate cell and genome damage used to decrease prostate cancer risk.

Intracellular Signaling Pathways and Prostate Cancer Treatment

Finally, progressive elucidation of the molecular mechanisms contributing to prostate

cancer cell growth, survival, and metastasis may lead to better treatments for established prostate cancer. Of course, androgen signaling pathways, essential for the growth and survival of most prostate cancer cells, have already been successfully targeted for prostate cancer treatment. However, despite treatment with androgen deprivation and/or anti-androgens, most men with advanced prostate cancer ultimately suffer cancer progression [van der Kwast et al., 1991; Amler et al., 2000; Feldman and Feldman, 2001; Mousses et al., 2001]. Since these progressive androgen-independent cancers appear to still use the androgen receptor to promote growth and survival, it is possible that the androgen receptor itself, and some of its post-translational modifications, might be even better targeted with new treatment approaches [Eder et al., 2002; Gioeli et al., 2002; Solit et al., 2002]. Also, several newly recognized signal transduction pathways offer new treatment possibilities. In particular, as described in this review, loss of PTEN function during prostate cancer progression implicates PI3K/Akt cell growth and survival signaling pathway in the development of life-threatening prostate cancer [Furnari et al., 1998; Ramaswamy et al., 1999; Sun et al., 1999]. Several new agents targeting various components of this pathway are under development for prostate and other cancers [Neshat et al., 2001; Podsypanina et al., 2001; Solit et al., 2002; Vivanco and Sawyers, 2002].

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