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Fingerprinting the Diseased Prostate: Associations Between BPH and Prostate Cancer

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Abstract Two of the most common diseases which occur in ageing men relate to their prostate. BPH and prostate cancer are prevalent diseases which have an impact on most men as they age. The advent of gene expression analysis has provided an opportunity to examine these diseases in a novel fashion. These analyses, to date, have revealed associations between these two diseases which have not been previously identified. These commonalities include global genetic changes which occur throughout the prostates in individuals with these diseases. Understanding the fingerprints of these diseases is providing novel markers and treatment strategies for both BPH and prostate cancer. J. Cell. Biochem. 91: 161–169, 2004. © 2003 Wiley-Liss, Inc.

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Prostate cancer (PCa) and benign prostatic hyperplasia (BPH) are two of the most common and devastating diseases affecting males. Although the diseases are not thought to be linked in their etiology, both involve growth disregulation of prostatic cells and therefore it is postulated that there may be some common genetic factors involved in disease onset and progression. Our laboratory has been interested in examining the genetic alterations associated with hyperplasia associated with both PCa and BPH. To investigate the genes, which may be involved in both of these disease processes, we have conducted a cDNA microarray analysis of human prostate tissue from normal, patients with BPH, as well as patients with PCa examining a variety of genes. Examination of the genes, which we have investigated as well as others in the field, reveals that patients with a severe form of BPH and patients with PCa exhibit similar genetic alterations, specifically involving primarily four categories of genes: growth regulatory genes, immunological genes, stromal associated genes, transcription factor/cell signaling genes, and genes whose functions remain unclear. To understand the etiology of these two diseases, it is necessary to examine the genes which are involved in progression or disease onset such that we can have a better understanding of the biology of both of these diseases as well as determine if a common pathway may be involved between BPH and PCa. In this review, we will describe the genes, which others and we have found to be up- or downregulated in normal versus diseased human prostate tissue.

BPH VERSUS PCa

Prostatic hyperplasia is a disease that afflicts the aging male population such that 75% of men over the age of 75 years are affected [Oesterling, 1996]. Benign prostatic hyperplasia (BPH) is defined as hyperplasia associated with both the stromal and epithelial compartments of the gland. Many clinical symptoms arise as a result of BPH, which significantly detract from the quality of life. These include urinary retention,

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post-void dribbling, painful urination, and ultimately renal failure; also chronic inflammation can result due to bacterial infection [Oesterling, 1996; Roper, 1998]. It is clear that BPH is actually more than one disease and often involves the prostate, bladder, and other organs in a complex mixture. To simplify our discussion here, we will focus on the prostatic alterations associated with the disease.

Historically much of the etiology of BPH has been attributed to the deregulation of androgen action but more recently it has been suggested that androgens alone may not be the sole contributing factor [Berthon et al., 1997]. A study by Wong and Wang [2000] implicates many growth factors to be involved in the progression and onset of disease. Because it is still unclear to the exact factors contributing to the pathophysiology of BPH, it is important to continue to investigate the etiology of BPH. Furthermore, the underlying molecular differences producing symptoms in some but not all patients with histologic BPH are largely unknown. The fact that BPH is confined to the transition zone of the prostate primarily and appears to not result in the formation of cancerous lesions remains poorly understood. Presently, disease onset and progression of BPH is not thought to be linked to the pathophysiology of PCa [De Marzo et al., 1999].

PCa is the most common malignancy among men in the United States and is the second leading cause of cancer-related deaths [De Marzo et al., 1999; Greenlee et al., 2001]. Several risk factors have been associated with an increased incidence of PCa. These factors include increasing age, a family history, African-American ethnicity, hormonal factors, as well as a diet, which is high in consumption of animal fat and red meat [Giovannucci, 1995; Whittemore et al., 1995; Kolonel, 2001]. The pathophysiology of PCa involves hyperplasia of the glandular compartment of the prostate. The pathogenesis of hyperplasia of the prostate in both of these diseases remains poorly understood. BPH predominantly arises in the transition zone of the prostate, whereas PCa predominantly arises in the peripheral zone of the prostate, secondly in the transition zone and followed by the central zone.

The prostate gland is a dynamic organ made up of a heterogeneous environment of both stromal and epithelial cells. The complexity of the interaction between both of these compartments has not been well elucidated. The association between these cellular types is critical to normal tissue regulation as well as being instrumental to these processes. Studies have shown that the stromal component may be directly contributing to the change in the hyperplasticity of the gland by secreting paracrine, autocrine, or other secretory peptides, which disrupt or alter the normal physiology of the gland. The epithelial cell layer consists of at least three cell types: basal, secretory, and neuroendocrine cells. The stromal compartment is made up of smooth muscle cells and fibroblasts primarily. These cells interact to maintain proper functioning, growth, and development of the gland.

Gene expression profiling facilitated by the development of DNA microarrays [Schena et al., 1995, Lockhart et al., 1996,] represents a major advance in global gene expression analysis. In a single assay, the quantitative expression of each gene in response to a change in the cellular state can be measured in parallel. In recent years, investigators have applied this technology in a variety of ways such as classification of disease samples, gene function during development and differentiation, target identification and validation, pathway dissection, and cellular responses to physiological [Tackels-Horne et al., 2001] perturbation or pharmacological treatment.

EPITHELIAL–STROMAL INTERACTIONS: FACTORS AND MECHANISMS OF ACTION IN GROWTH REGULATION

Epithelial–stromal interactions are important not only in the growth, development, and functional cellular differentiation of the normal prostate but also in abnormalities of the prostate gland such as BPH and prostate carcinoma (PCa). A study conducted by Cunha et al. [1983] showed that stromal cells have the ability to modulate the differentiation pattern of normal prostatic epithelium. Other studies have shown that growth factors produced by both the epithelial and stromal cells can regulate the alternate cell type. The prostatic stroma contains many cellular components including smooth muscle cells, fibroblasts, blood vessels, and nerve fibers.

The stromal cells are responsible for secreting many growth factors such as fibroblast growth factors, insulin-like growth factors I and II, as well as tumor growth factors, which act in an

autocrine manner on the stroma itself as well as the neighboring glandular cells to induce proliferation. Other components, which are thought to be involved in growth regulation and are secreted by the prostate cells are matrix metalloproteinases (MMPs). The production of MMPs by prostatic epithelial and/or neighboring stromal cells gives cells the capability to penetrate extracellular matrix barriers in normal or neoplastic growth. [Wilson et al., 2002] One of the organs believed to be influenced by the EGF system is the prostate gland. Growth of the prostate can lead either to a hyperplastic growth of the gland or to PCa. Growth factors from the EGF system have been shown to be responsible for autocrine stimulation of PCa cells. Furthermore, stimulation with EGF induces proliferation of epithelial cells derived from the prostate. Proliferation of stromal cells from the prostate has also been shown to be increased by growth factor stimulation. In the prostate, the EGF system has also been suggested to play an important role for stroma–epithelium interactions. [Sorensen et al., 2000]. The role of the stroma in PCa progression has also been suggested. In carcinomas, marked changes in stromal–epithelial interactions are frequently seen at the invading front. The basement membrane is a boundary that is not breached by normal epithelial cells. However, cancer cells cross this boundary and invade the underlying stroma where a reaction is mounted by stromal cells against the invading cancer cells. As a result of this stromal–cancer cell interaction, lasting changes occur in the normal epithelial–stromal interactions. It appears that due to the altered characteristics of cancer cells, such as excessive production and secretion of growth factors and proteases, changes in stromal cell behavior are induced which may actually enhance the motility and invasion by cancer cells. The interactions between the stromal and epithelial compartment of the prostate are clearly important in both the normal and abnormal growth of the gland. It is imperative to study the specific mechanisms, which these factors affect to elucidate the exact etiology of the gland.

ANDROGEN REGULATION OF THE PROSTATE

During development, androgens and the androgen receptor regulate several key events that include development and differentiation of major target tissues such as the prostate, seminal vesicles, and epididymis. Furthermore, it is generally held that androgens are not only required for normal function of the prostate gland but also have been implicated in prostate disease as well [Lee, 1996]. Thus identifying target genes that are androgen-regulated may help to better understand the molecular basis of prostate physiology during health and disease.

The role of androgens in the prostate is an important one. Studies have shown that both normal as well as diseased physiology of the prostate is dependent upon androgen action via the androgen receptors. In the developing prostate, the effects of androgens have been demonstrated to be primarily on the underlying stromal cells, which are the only cell type to contain androgen receptors during this stage [Cunha et al., 1983]. As the prostate matures, androgen receptors are found in both epithelial and stromal cells and therefore androgen action at this time may occur directly in both [Sar et al., 1990]. 5α-reductase, the enzyme that is responsible for the conversion of testosterone to dihydrotestosterone, is only localized in the stromal cells, again demonstrating the importance of stromal cells in the hormonal regulation of prostatic growth. The ligand-androgen receptor complexes that exist have been shown to affect prostatic function by interacting with androgen responsive elements (AREs), which are specific DNA sequences located in the regulatory regions of a number of genes. In addition, DHT has been demonstrated to also influence the expression of other prostatic growth factors. In support of evidence that androgens are required for disease progression, it has been known that men who are castrated prior to onset of puberty do not develop BPH or PCa. Also, both epithelial and stromal cells of the prostate are responsive to steroids such as androgens and estrogens.

The genetic alterations associated with severe BPH and PCa have been examined using cDNA microarray analysis [Prakash et al., 2002]. We have found that numerous genes identified in our analysis had a similar trend between both severe BPH and patients with PCa. Symptomatic BPH in itself appears to be closely related to PCa since both diseases involve an increase in a deregulation of prostatic growth control. It has been suggested that tumor development proceeds by a process

analogous to Darwinian evolution in which a succession of genetic changes, each conferring some growth advantage, leads to the progressive conversion of normal human cells into cancer cells [Hanahan and Weinberg, 2000]. Unlike PCa, however, BPH is rarely associated with genetic abnormalities and is an overgrowth of a more normal epithelium [De Marzo et al., 1999]. Our present study suggests that BPH, like PCa, also has distinct genetic alterations, which may provide for a clearer understanding of the basis for disease. The genes, which are upregulated in both BPH and PCa, are summarized in Table I. This finding is of particular interest because to date both of these diseases are said to be independent of each other. But due to the similarity in gene alterations in the 47 genes described here, it is postulated that the etiology of the diseases may have some coinciding factors, which remain unclear. Upon further examination of the listed genes, it is observed that four obvious gene types are exhibited: growth regulatory genes, immunological/inflammatory genes, transcription/cell signaling genes, stromal component genes, and a few of unknown function. We also investigated genes, which are downregulated in the diseased prostate (Table II). Similarly, we have found that genes, which are downregulated in BPH patients, are also downregulated in patients with PCa. Interestingly, the trend for each of these genes is amazingly consistent. These findings further support a common genetic etiology between the two diseases. We have categorized the genes, which are up/downregulated in the diseased prostate according to their function. In addition to our findings, other investigators have examined gene alterations between normal and diseased prostate, particularly in PCa. We will describe how our findings coincide or differ with the described studies.

TABLE I. Genes Upregulated in BPH and Cancer

Gene name	BPH with symptom	BPH-fold change from normal patients	Cancer	Cancer-fold change from normal patients
B-cell homing chemokine (ligand for Burkitt's lymphoma receptor	715	35.75	270.00	13.50
JM-27	2747	17.78	1234.00	7.99
Collagen, type XIII, alpha-1	306	12.24	210.00	8.40
v-Fos FBJ murine osteosarcoma viral oncogene homolog	1187.8	13.29	1709.00	19.12*
Nel (chicken)-like 2	617.5	6.38	425.00	4.39*
Early growth response 1	440.2	6.35	971.00	14.01*
MHC, class II, DP beta-1	415.3	5.52	203.00	2.70
Insulin-like growth factor binding protein 10	302	5.29	908.00	15.90*
Retinol-binding protein 1, cellular	819	4.90	341.00	2.04
Complement component 7	567.4	4.67	574.00	4.72
Erythropoietin receptor	363	4.20	158.00	1.83
Matrix metalloproteinase 23A	1383	4.14	1191.00	3.57
Procollagen C-endopeptidase enhancer	767.3	4.11	618.00	3.31
Lumican	831.6	3.89	782.00	3.66*
Immediate early protein	1279	3.80	2244.00	6.67*
P311 protein	379.9	3.74	405.00	3.99
Tumor necrosis factor receptor superfamily, member 7	202	3.61	268.00	4.79*
Jun activation domain binding protein	4249	3.60	4537.00	3.84*
Small inducible cytokine A5 (RANTES)	389	3.60	211.00	1.95
Coagulation factor C (Limulus polyphenus) homology	820	3.39	503.00	2.08
Jun-B proto-oncogene	1090.9	3.38	1868.00	5.79*
Elastin (supravalvular aortic stenosis, Williams–Beuren syndrome)	902.9	3.38	746.00	2.79
Transcription factor 21	617	3.30	521.00	2.79*
Decorin, signal sequence receptor, alpha (translocon-associated protein alpha)	1509	3.27	952.00	2.07
K1AA1112 protein	869	3.15	256.00	0.93
D component of complement (adipsin)	1950	3.10	1040.00	2.21
Cysteine and glycine-rich protein 2 (LIM domain only, smooth muscle)	486.00	2.99	225.00	1.38

Fold changes were determined by taking median values for each group in comparison to the normal patients. All fold changes associated with BPH with symptom patients were significantly greater than normal patients. An asterisk (*) indicates significant fold change (P-value < 0.05) in the cancer patients in comparison to normal patients.

TABLE II. Genes Downregulated in BPH and Cancer

Gene names	BPH with symptom	Fold change from normal	Cancer	Fold change from normal
Hexokinase 2	51	−3.0	58	−2.7*
Period (*Drosophila*) homolog 1	95	−3.2	308	−1
Prostate differentiation factor	279	−3.2	1127	−0.8
UNC13 (*C. elegans*)-like	107	−3.2	77	−4.4
Ras-GTPase activating protein SH3 domain-binding protein 2	144	−3.2	322	−1.4
Angiotensinogen	64	−3.2	29	−7.0
Metallothionein 1L, metallothionein 1X	643	−3.3	624	−3.4*
Monoamine oxidase A	1183	−3.4	1304	−3.1
Pre-B-cell colony enhancing factor	79	−3.5	159	−1.7
Transcription factor 8	52	−3.6	254	−0.8
s-Adenosylmethionine decarboxylase 1(1)	78	−3.6	148	−1.9
Interferon-stimulated gene (20 kD)	63	−3.5	111	−2.0*
Superoxide dismutase 2, mitochondrial	436	−3.7	742	−2.2
Metallothionein 1G	375	−4.0	356	−4.2
Ornithine decarboxylase 1	160	−4.1	455	−1.5
s-Adenosylmethionine decarboxylase 1 (2)	124	−4.7	196	−3.0*
H1 histone family, member 2 (1)	193	−4.8	364	−2.6
Progastricsin (pepsinogen C)	35	−5.4	89	−2.1
Myosin, light polypeptide 2, regulatory, cardiac, slow	48	−6.6	38	−8.4
Calsequestrin 2, cardiac muscle	20	−8.7	20	−8.7*
H1 histone family, member 2 (2)	204	−2.7	348	−1.6
H1 histone family, member 2 (3)	34	−9.1	105	−2.9

Fold changes were determined by taking median values for each group in comparison to the normal patients. All fold changes associated with BPH with symptom patients were significantly greater than normal patients. An asterisk (*) indicates significant fold change (P-value < 0.05) in the cancer patients in comparison to normal patients.

ALTERED EXPRESSION OF GENES IN THE HYPERPLASTIC PROSTATE

Growth Regulatory Genes

Analyses of several genes, which are associated with growth regulation, were significantly upregulated in both the symptomatic BPH and PCa patients. These genes include neural epidermal growth factor-like 2 (nel-like 2) [Luce and Burrows, 1999], which may be involved in cell growth regulation and differentiation as it contains epidermal growth factor (EGF)-like repeats, early growth response 1, which has been implicated as a tumor suppressor as well as involved in mitogenesis [Fujino et al., 2003] and insulin-like growth factor binding protein 10, which is an immediate early gene and is involved in downstream activation via growth factors and involved in cell adhesion and migration [Kim et al., 2003]. The ornithine decarboxylase 1 gene, which is a universal marker to detect proliferation, was significantly downregulated in the prostates of the BPH with symptom patients but not in the cancer prostate tissue [Ike et al., 2002; Bachrach and Wang, 2003].

Transcription Factors/Cell Signaling Genes

Transcriptional regulatory genes play a significant role in disease progression particularly in tumorigenesis. Our present study indicates that such gene alterations are also associated with hyperplasia of the prostate in symptomatic BPH as well as in PCa. Upregulated genes of this type include, v-fos FBJ murine osteosarcoma viral oncogene homolog, which is considered the strongest activator of the AP-1 transcription factor complex [Acquaviva et al., 2002] and jun activation domain binding protein (JAB1), which is involved as a coactivator of AP1 transcription factor [Chauchereau et al., 2000]. Genes which we found to be upregulated in symptomatic BPH patients but not in cancer tissue include retinol-binding protein 1, which regulates vitamin A transport and binding to nuclear receptors [Esteller et al., 2002], erythropoietin receptor, which cooperates in regulating blood cell development [Damen and Krystal, 1996]. Other genes that are involved in transcriptional regulation which were found to be significantly downregulated in both symptomatic BPH and in PCa patients include, hexokinase 2, which is involved in metabolic pathways [de la Cera et al., 2002] and period homolog 1, which belongs to the human clock gene family. We have found some of the genes in our study were only significantly downregulated in symptomatic BPH patients such as the UNC13 gene, which is a homolog to the diacylglycerol-binding protein [Xu et al., 1998], the Ras-GTPase activating protein SH3 domain-binding protein 2 gene, which

negatively regulates GTPases Ehrhardt et al., 2002), and finally, transcription factor 8 (PAX-8), which encodes for transcription factors required for development of various tissues [Di Palma et al., 2003]. The above-described genes demonstrate that transcriptional regulatory genes are important in prostatic hyperplasia associated with both BPH and PCa tissue.

Genes Encoding Immunological Products

Genes that encode proteins that are involved in the immunological response are particularly interesting to evaluate in hyperplasia associated with BPH and PCa. Our findings exhibit that both diseases involve up- or downregulation of genes that correspond to the body's defense mechanisms in response to diseased tissue. Several gene types have been investigated in this study, which are shown to be upregulated in BPH and PCa in comparison to normal prostate. These gene types include, tumor necrosis factor receptor superfamily, member 7, which has been suggested to play a role in activation and survival of T-cells as well as the apoptosis signaling pathway (GeneBank, NCI), B-cell homing chemokine is involved in migration of leukocytes during inflammation as well as has been implicated in homing of lymphocytes [Gunn et al., 1998], MHC, class II, DP beta, which belongs to the HLA class II beta chain molecules seems to play a central role in antigen presentation to antigen presenting cells [Rajsbaum et al., 2002], and finally, complement component 7 is an immune effector that can eliminate foreign cells, both in virally infected cells and cancer cells [Oka et al., 2001]. Several genes involved in the immunological response are downregulated in the diseased prostate tissue in comparison to normal prostate. These genes include, pre-B-cell colony enhancing factor that is involved in maturation of B-cell precursors [Ognjanovic and Bryant-Greenwood, 2002]. The interferon-stimulated gene, which has many effects depending on the cell type and state of differentiation including transcriptional regulation and immune response [Perry et al., 1999] was significantly downregulated in the diseased prostate tissue in this study.

Stromal Component Genes

As described earlier in this review, the prostate gland is a heterogeneous environment composed of both a stromal and epithelial component and interactions between the two cell types have been implicated in normal and diseased prostate growth and differentiation. Several genes encoding proteins, which are considered to be stromally associated, have been investigated in the present study and found to be altered in expression. Genes of this type that are upregulated include; collagen, type XIII collagen, which is found at many sites of cell adhesion in tissues. [Kvist et al., 2001], matrix metalloproteinase 23A, which is involved in breakdown of the extracellular matrix [Nagase and Woessner, 1999], procollagen C-endopeptidase enhancer, which is an extracellular matrix glycoprotein and enhances activities of proteinases [Rattenholl et al., 2002], lumican, which a major component of keratin sulfate proteoglycan of various tissue including the bone matrix [Raouf et al., 2002], P311 protein gene, which is involved focal adhesions [Mariani et al., 2001], elastin, which encodes for a fiber found in the stroma [Kozel et al., 2003], the decorin gene, which is a small proteoglycan and extracellular matrix protein found in many connective tissues [Scott et al., 2003], D component of complement (adipsin), which is an adipocyte secreted protein [Miner et al., 2001], and the cysteine and glycine-rich protein 2 gene, which is proposed to function as a molecular adapter [Weiskirchen et al., 2001]. Certain stromally associated genes in our study were also downregulated in the diseased prostatic tissue in comparison to normal tissue. Genes of this type include the myosin, light polypeptide 2 myosin light chain 2 (MLC2) gene, which is one of the important myofibrillar proteins involved in the regulation of myofilament calcium (Ca^{2+}) sensitivity and cardiac entropy [Kanaya et al., 2003], the calsequestrin 2 gene, which is a sarcoplasmic reticulum protein [Frank et al., 2001].

Uncategorized/Function Unknown

A large number of the genes identified in our analysis encode proteins of unknown function. An interesting example of this type of gene is that encoding JM-27. This gene product has been found to be specifically expressed in male and female urinogenital tract tissue including the prostate gland and uterus [Prakash et al., 2002]. Our laboratory has been particularly interested in the role of this gene in the prostate gland and disease progression. We have been able to investigate the expression of the JM-27

protein in normal and diseased tissue using an antibody we have generated against a synthetic peptide. Our findings indicate that expression of the JM-27 protein is also upregulated in symptomatic BPH tissues as well in adjacent PCa tissues. The expression of the protein is isolated to the stromal component of human tissue and therefore JM-27 may be a stromal factor that plays a regulatory role in prostate growth. Further investigations in our laboratory show that the expression of this protein is androgen-regulated using a rat castration model of study (data not shown).

Androgen-regulated genes are of particular interest in the prostate gland due to the nature of both BPH and PCa being dependent upon androgens for growth and differentiation eventually leading into androgen-independent states of disease. It is our goal to continue studies to extrapolate on our gene array studies to determine the actual roles of each of these altered genes in prostatic hyperplasia associated with both BPH and PCa.

CONCLUSIONS

Gene expression analysis by DNA microarray technology has allowed us to investigate alterations in thousands of genes in diseased versus normal prostatic tissues. Genetic alterations associated with hyperplasia in the diseased prostate both in BPH and PCa have been an ongoing interest in our laboratory as well as others. The data revealed in these analyses provide potential targets for biomarkers, as well as a method to classify states of the disease. By examining genes that are similarly altered in both BPH and PCa, a common or parallel pathway of disease progression or onset may be determined. One major criticism to this new technology is that numerous groups may conduct such studies and each group in turn may find a different set of genes, which are altered. Comparisons of genetic alterations associated with prostatic hyperplasia from our study and others reveal many such differences. It is important, however, to realize that the tissue sample sets were significantly different in our study from the others described in this review. The studies conducted by Rhodes et al. [2002] used two sample groups: clinically localized PCa and benign prostate tissue. In their study the benign prostate tissue group also contained BPH tissue and it was not distinguished from benign tissue. Our findings indicate that prostatic hyperplasia associated with a severe form of BPH and PCa do exhibit similarities in genetic alteration particularly in the growth regulatory gene category. Despite the differences in the cell types, and location of the hyperplasia in both BPH and PCa, the growth regulatory genes-nel-chicken like 2, early growth response1, and insulin-like-binding protein 10 are disregulated in both disease states. These analyses provide a provocative insight into the mechanisms, which underlie these highly prevalent diseases of men and suggest that there may be a number of common links between them.

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