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Research Highlights

Prostate News

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Pokemon's central role in cancer development

Researchers at New York's Memorial Sloan-Kettering Cancer Center report novel findings in *Nature* regarding a new cellular oncogene implicated in the development of human cancers, including prostate neoplasia. Pokemon, a pop-culture inspired acronym for 'POK erythroid myeloid ontogenic factor', is a POK protein family member encoded by the *ZbTb7* gene and characterized by its critical transcription function in cellular differentiation. Takahiro Maeda, Pier Paolo Pandolfi and colleagues show that Pokemon acts as a genuine proto-oncogene when overexpressed by inhibiting the expression of tumor suppressors, such as ARF.

To establish this novel finding, the authors conducted a complete battery of genetic, clinical, and pathological proofs. They first assessed the role of Pokemon in cancer pathogenesis via a direct genetic approach. Using classic cell growth and transformation assays, they found that mouse embryonic fibroblasts lacking *ZbTb7* are completely refractory to oncogene-mediated cellular transformation. The characterization of putative Pokemon-binding sites revealed that Pokemon is a key ARF transcriptional repressor, and specifically a potent repressor of the $p19^{Arf}$ tumor supressor gene. Pokemon is also oncogenic *in vivo*, as the authors demonstrate in a transgenic mouse model. Tissue microarray analyses in breast, lung, colon, bladder, and prostate tumors further corroborated the oncogenic nature of the transcription factor in human cancers. The authors find that Pokemon is overexpressed in human cancers, and these expression levels may be used to predict the clinical outcome. These results provide strong rationale for the development of the transcription-based therapeutic strategies and establish Pokemon's critical role in oncogenesis.

Original Research Paper

Maeda T *et al*. Role of the proto-oncogene *Pokemon* in cellular transformation and ARF repression. *Nature* 2005; **433**: 278–285.

Epigenetics: freedom of gene expression

Long-Chen Li, Peter Carroll, and Rajvir Dahiya pose incisive questions designed to clarify the biological significance and consequence of epigenetic processes in prostate cancer in their review for the *Journal of the National Cancer Institute*. Genetic alterations (mutations) and epigenetic aberrations (heritable changes in gene expression that occur without changes in DNA sequence) appear to contribute to the malignant transformation and progression of prostate cancer. Epigenetic changes are reversible, which make them attractive targets for cancer treatment with modulators that demethylate DNA and inhibit histone deacetylases, leading to reactivation of silenced genes. DNA methylation and histone modifications are important epigenetic mechanisms of gene regulation, and both play essential roles in tumor initiation and progression. In prostate cancer, aberrant epigenetic events such as DNA hypo- and hypermethylation and altered histone acetylation have been observed to affect a large number of genes. However, no plenitude is without peril: although the number of genes that undergo aberrant epigenetic inactivation associated with prostate cancer seems to be growing, very few of these genes have yielded promising results as potential tumor biomarkers for early diagnosis and risk assessment. In order to identify prostate cancer-specific epigenetic fingerprints, the authors stress that large-scale screening of significant epigenetic events is needed.

Review

Li L-C *et al*. Epigenetic changes in prostate cancer: implication for diagnosis and treatment. *J Natl Cancer Inst* 2005; **97**: 103–115.

Diabetes and the risk of prostate cancer

An association between diabetes and prostate cancer has been previously proposed, with one study suggesting that diabetes may decrease the risk of developing prostate cancer, but only several years after initial diabetes diagnosis. Epidemiologists at the American Cancer Society evaluate this putative link in the January issue of the *American Journal of Epidemiology*. Carmen Rodriguez *et al* examine diabetes diagnosis timing and its relation to prostate cancer risk among men enrolled in the Cancer Prevention Study II Nutrition Cohort. Participants in this prospective cohort completed questionnaires designed to garner information on diabetes status at enrollment in 1992, and again at follow-up points in 1997 and 1999. A previous study conducted in 1982 provided further historical information. In all, the authors document 5318 cases of incident prostate cancer among a total of 72 670 men. Results show that diabetes is associated with a lower incidence of prostate cancer (rate ratio (RR) = 0.67, 95% confidence interval (CI): 0.60, 0.75). However, this association differs significantly by time since diagnosis of diabetes—risk of prostate cancer was slightly increased during the first 3 y after diagnosis of diabetes (RR = 1.23, 95% CI: 0.56, 0.71), but reduced among men diagnosed 4 y or more earlier. These

epidemiological results are clearly consistent with the hypothesis that prostate cancer risk is reduced in men with well-established diagnoses of diabetes.

Original Research Paper

Rodriguez C *et al*. Diabetes and the risk of prostate cancer in a prospective cohort of US men. *Am J Epidemiol* 2005; **161**: 147–152.

Bone metastates and prostate cancer

Prostate cancer is unique in that bone is often the only clinically detectable site of metastasis. The resulting tumors tend to be bone-forming (osteoblastic) rather than bone-lysing (osteolytic), thus leading to pain and compression of the spinal cord. In *Nature Reviews Cancer*, Christopher Logothetis and Sue-Hwa Lin review the association of prostate cancer with bone metastases, detailing extant clinical observations and future directions for treatment strategies. Bone metastases with a bone-forming phenotype are the result of stimulation of osteoblasts or inhibition of osteoclasts by cancer cells. Prostate cancer cells produce factors that perturb the bone microenvironment in ways that affect the normal balance between osteoblast and osteoclast activities, thereby resulting in osteoblastic metastases. Osteoblasts themselves also secrete factors that facilitate the progression of prostate cancer to bone. The authors further discuss the biology of metastasis to bone, and ask whether this knowledge can point to new therapeutic strategies for prostate cancer.

Review

Logothetis CJ, Lin S-H. Osteoblasts in prostate cancer metastasis to bone. *Nat Rev Cancer* 2005; **5**: 21–28.

Mechanisms of action: Taxotere and Furtulon

There is a tremendous need for the development of efficient, targeted strategies for the treatment of prostate cancer, especially as many patients fail to respond to androgen-ablative therapy or experience relapse after radical prostatectomy. Docetaxel, a chemotherapeutic agent known commercially as Taxotere, has been shown in clinical trials to confer beneficial clinical response when administered weekly to patients with metastatic hormone-refractory prostate cancer. Capecitabine, an orally administered systemic prodrug of doxifluridine (5′-deoxy-5-fluorouridine (5′-DFUR), or Furtulon), has also displayed antitumor activity in various cancers. Taken in combination, these drugs have exhibited high anticancer activity in advanced breast cancers. Yet although it is known that docetaxel binds to microtubules whereas capecitabine is incorporated into DNA, the precise molecular mechanisms by which these drugs inhibit cancer cell proliferation are not known. In order to elucidate these mechanisms of action, Yiwei Li and colleagues use high-density DNA microarray analysis containing 22 215 known genes to determine the alteration of gene expression profiles of hormone insensitive (PC3) and sensitive (LNCaP) prostate cancer cells exposed to docetaxel and doxifluridine. Their results, published in *BioMed Central Cancer*, show that both agents downregulated several genes critical for cell proliferation, cell cycle progression, transcription factor, cell signaling and oncogenesis. Moreover, docetaxel and doxifluridine were found to upregulate some genes responsible for chemotherapeutic resistance. The authors suggest that these data may provide the foundation for further research on the mechanisms by which docetaxel and doxifluridine exert their pleiotropic effects on prostrate cancer cells, and perhaps aid in the development of mechanism-based targeted therapeutic strategies against prostate cancer itself.

Original Research Paper

Li Y *et al*. Gene expression profiling revealed novel mechanism of action of Taxotere and Furtulon in prostate cancer cells. *BMC Cancer* 2005; **5**: 7 (doi.10.1186/1471-2407-5-7).

Androgen receptor as proto-oncogene in prostate cancer

Since androgen receptor (AR) expression is found in nearly all prostate cancers, both before and after androgen ablation therapy, it is likely that AR activity contributes to all stages of prostate cancer progression. Global gene expression profiling studies have shown AR to be the only gene consistently upregulated in therapy-resistant human prostate cancer xenografts, and AR gene amplification after androgen ablation therapy has been reported in almost one-third of prostate tumors. Furthermore, many recurrent prostate cancers overexpress coactivators that can increase AR activity in the presence of physiological levels of adrenal androgen, and some growth factor pathways have even been found to activate AR in the absence of androgen. Whereas the mutation, amplification, overexpression of AR, or crosstalk between AR and other growth factor pathways may explain the failure of androgen ablation therapies in some cases, there is little evidence supporting a causal role between AR and prostate cancer. In a study for the *Proceedings of the National Academy of Sciences*, Guangzhou Han and others functionally and directly address the role whereby AR contributes to spontaneous cancer progression by generating transgenic mice expressing: AR-WT to recapitulate increased AR levels and ligand sensitivity; AR-T857A to represent a promiscuous AR ligand response; and AR-E231G to model altered AR function. Whereas transgenes encoding either AR-WT or AR-T857A did not cause prostate cancer when expressed at equivalent levels, expression of AR-E231G, which carries a mutation in the most highly conserved signature motif of the NH(2)-terminal domain, caused rapid development of prostatic intraepithelial neoplasia that progressed to invasive and metastatic disease in 100% of mice examined. Overall, these data demonstrate the oncogenic potential of steroid receptors and implicate altered AR function and receptor coregulator interaction as critical determinants of prostate cancer initiation, invasion, and metastasis.

Original Research Paper

Han G *et al*. Mutation of the androgen receptor causes oncogenic transformation of the prostate. *Proc Natl Acad Sci* 2005; **102**: 1151–1156.

Etiology and severity of prostate cancer linked to *CYP3A* genes

Members of the cytochrome *P*450 3A (CYP3A) subfamily are notable for their ability to metabolize a diverse range of endogenous substrates and clinically important exogenous compounds. Additionally, the enzyme products of two *CYP3A* genes, *CYP3A4* and *CYP3A5*, are clearly involved in testosterone metabolism and have been previously associated with prostate cancer occurrence and severity. In order to examine the effects of these genes on the etiology and severity of prostate cancer, Charnita Zeigler-Johnson *et al* report in *Cancer Research* their evaluation of genotypes and haplotypes of *CYP3A*4, *CYP3A5* and *CYP3A43* on the bases of ethnicity and tumor characteristics. In order to comprehensively examine the effects of these genes on prostate cancer occurrence and severity, the authors studied 622 incident prostate cancer cases and 396 controls. Substantial and race-specific linkage disequilibrium was observed between *CYP3A4* and *CYP3A5*, but not between other pairs of loci; there was not, however, an association of *CYP3A5* genotypes with prostate cancer or disease severity. *CYP3A43**3 was associated with family history-positive prostate cancer, while *CYP3A4*1B* was associated inversely with the probability of having prostate cancer in Caucasians. Significant interactions among these loci associated with prostate cancer occurrence and severity were also observed. The combined observations that *CYP3A4* and *CYP3A43* are associated with prostate cancer, are not in linkage equilibrium, and are both involved in testosterone metabolism suggest that both *CYP3A4*1B* and *CYP3A43**3 may influence the probability of having prostate cancer and experiencing severe disease progression. The authors conclude that, combined with information about the function of these genes, there is growing evidence that one or more of the genes in the CYP3A locus are involved in the etiology of prostate cancer.

Original Research Paper

Zeigler-Johnson C *et al*. *CYP3A4*, *CYP3A5*, and *CYP3A43* genotypes and haplotypes in the etiology and severity of prostate cancer. *Cancer Res* 2004; **64**: 8461–8467.

Xenoestrogen action in prostate cancer

Androgen is critical for prostate development, growth, and survival. Therapies for advanced prostate cancer aim to block androgen receptor (AR) action, but recurrent tumors harboring restored AR activity ultimately do arise. One mechanism of such reactivation occurs through AR mutations, rendering the receptor responsive to noncanonical ligands. Yelena Wetherill *et al* have previously shown that a known xenoestrogen, bisphenol A (BPA), activates a tumor-derived AR mutant (*T877A*), leading to androgen-independent prostate cancer cell proliferation. In an article for *Cancer Research*, these same authors demonstrate that BPA cooperates with androgen to activate AR-T877A, as shown by both reporter assays and increased levels of PSA expression. Investigations using both yeast and mammalian model systems revealed that multiple AR alleles are responsive to BPA, thus expanding the potential influence of xenoestrogens on prostate cancer. Moreover, *in vitro* radioligand-binding assay showed that BPA alters 5α-dihydrotestosterone binding to AR-T877A, likely through noncompetitive inhibition. Higher concentrations of BPA blocked proliferation of AR-positive, androgen-dependent prostate adenocarcinoma cells (LNCaP and LAPC-4), and had a more modest inhibitory effect on androgen-independent cells (22Rv-1). By contrast, AR-negative prostate cancer cells failed to show growth inhibition after exposure to high BPA dose. The authors conclusively show that BPA can serve as a potential 'hormone sensitizer' of the mutant ARs present in advanced prostate adenocarcinomas, thereby perhaps contributing to therapeutic relapse in advanced prostate cancer patients. These results corroborate the notion that nonsteroidal environmental compounds can alter the function of nuclear receptor complexes.

Original Research Paper

Xenoestrogen action in prostate cancer: pleiotropic effects dependent on androgen receptor status. *Cancer Res* 2005; **65**: 54–65.

SUO redefines management of HRPC

The Society of Urologic Oncology (SUO) convened a multidisciplinary panel of urologists, oncologists, and radiation oncologists to develop a treatment algorithm for patients with hormone-refractory prostate carcinoma (HRPC), as reported in *Cancer*. Management of HRPC presents a unique challenge for the clinician, as patients form a diverse population, both demographically and clinically. Yet, despite a wealth of research on the management of HRPC, the authors found that few published studies have provided definitive treatment answers. Based on a review of current literature, along with the expert opinions of SUO's panelists, the multidisciplinary team sought to remedy this lack by producing an HRPC treatment guideline. The article provides a logical progression of treatment choices that include hormonal manipulations, chemotherapeutic options, and adjunctive therapies. Future clinical trials and therapies are also discussed. Although significant progress has been made in understanding and treating hormone-refractory prostate carcinoma, the authors stress that earlier interventions are ideal and that management strategies should be tailored to the individual patient.

Review

Chang SS *et al*. Society of Urologic Oncology position statement: redefining the management of hormone-refractory prostate carcinoma. *Cancer* 2005; **103**: 11–21.

Perinatal imprinting and adult prostate cancer

The fetal-origin hypothesis, first proposed in 1989, states that perinatal events are 'imprinted' on the developing organism and may affect pathogenesis of chronic disease in adulthood. A well-known example of this phenomenon is illustrated by the case of daughters born to women

exposed to the nonsteroidal estrogen diethylstilbestrol (DES) during early pregnancy—daughters displayed epithelial dysplasia in the upper vagina, with significantly increased risk of developing adenocarcinoma of the cervix and vagina. Analogously, DES also disturbs prostatic development, alters epithelial cell differentiation, and has been shown to predispose mice to prostatic intraepithelial neoplasia in later life. In an article for the *Proceedings of the National Academy of Sciences*, Yoko Omoto and colleagues investigate the biological mechanisms underlying imprinting of the neonatal ventral prostate, with particular attention to estrogens and the mediating role of estrogen receptors (ER). Using ER$\alpha^{-/-}$ and ER$\beta^{-/-}$ knockout mice, the authors found ERα abundantly expressed in the stroma of the mouse ventral prostrate during the first week of life, but expressed exclusively in the prostatic epithelium by the second and third weeks; by week four, ERβ was dominant. These data suggest that imprinting of the neonatal mouse ventral prostate is mediated by estrogen acting directly on epithelial and stromal ERα during the first 2 weeks of life. If this animal model proves to be analogous to human development, ERα could be an appropriate target in reducing epithelial proliferation in prostate carcinoma.

Original Research Paper

Omoto Y *et al.* Estrogen receptor α and imprinting of the neonatal mouse ventral prostate by estrogen. *Proc Natl Acad Sci USA* 2005; **102**: 1484–1489.

Commentary

Söder O. Perinatal imprinting by estrogen and adult prostate disease. *Proc Natl Acad Sci USA* 2005; **102**; 1269–1270.

Survival outcomes from a large population-based cohort

In order to decide on screening strategies and curative treatments for prostate carcinoma, it is necessary to determine the incidence and survival in a population that is not screened. To this end, Gunnar Aus and colleagues analyzed 15-y projected survival data from a prospective, population-based registry of 8887 patients with newly diagnosed prostate carcinoma from 1987 to 1999. Their results, which appear in *Cancer*, indicate that the median patient age at diagnosis was 75 y (within a range of 40–96 y), and that 12% of patients were diagnosed before the age 65 y. For patients who remained alive, the median follow-up was 80 months. In total, 5873 of 8887 patients (66.1%) died, and 2595 of that number (44.2%) died due to prostate carcinoma. The overall median age at death was 80 y (range: 41–100 y). The projected 15-year disease-specific survival rate was 44% for the whole population. In total, 18% of patients had metastases at diagnosis (M1), and their median survival was 2.5 y. Patients with nonmetastatic T1–T3 prostate carcinoma had a 15-year projected disease-specific survival rate of 66%. Patients who underwent radical prostatectomy experienced a significantly lower risk of dying from prostate carcinoma (relative risk: 0.40) compared with patients who were treated with non-curative therapies or radiotherapy. The authors conclude that the disease-specific mortality was comparatively high, but it took 15 y to reach a disease-specific mortality rate of 56%. These data form a truly population-based baseline on how prostate carcinoma will affect a population when screening is not applied, and can be further used for comparison with other health-care strategies.

Original Research Paper

Aus G *et al.* Survival in prostate carcinoma—outcomes from a prospective, population-based cohort of 8887 men with up to 15 years of follow-up. *Cancer* **103**: Early View (13 Jan 2005) (doi.10.1002/cncr.20855).

Life after brachytherapy: impact of BMI, ERBT, and ADT on biochemical outcome

Gregory Merrick and colleagues have evaluated the impact of body mass index (BMI), external beam radiotherapy (ERBT) and androgen deprivation therapy (ADT) on the 8-y biochemical outcome after permanent prostate brachytherapy. Their results, appearing in both the *International Journal of Radiation Oncology Biology Physics* and *Urology*, provide an inclusive picture of issues related to radioactive 'seed' therapy. In both studies, 668 consecutive patients underwent brachytherapy using either ^{103}Pd or ^{125}I for clinical Stage T1b–T3aNxM0 adenocarcinoma of the prostate gland. No patient underwent seminal vesicle biopsy or lymph node staging. The median follow-up was 59.5 months.

In evaluating ERBT and ADT, biochemical progression-free survival was defined by the American Society for Therapeutic Radiology and Oncology's consensus definition. For the entire group, the actuarial 8-y biochemical progression-free survival rates were 98.2, 98.4, and 88.2% for low-, intermediate-, and high-risk patients, respectively, with a median PSA level of <0.1 ng/ml for all risk groups and ADT and EBRT subgroups. The authors conclude that prostate brachytherapy results in a high probability of 8-y biochemical progression-free survival for low-, intermediate-, and high-risk patients. Although the role of supplemental EBRT cannot be adequately evaluated in high-risk patients, it does not appear to improve biochemical outcome in low- and intermediate-risk patients. However, ADT does result in a statistically significant improvement in progression-free survival for high-risk patients.

For the examination of BMI associations with biochemical outcome, progression-free survival was defined by a PSA level of 0.4 ng/ml or less after a nadir. In this case, the 8-y biochemical progression-free survival rates were 95.8, 95.6, 94.1, and 100% for patients in BMI categories less than 25, 25.0–29.9, 30.0–34.9, and 35 or more kg/m^2, respectively. In hormone-naive and hormone-manipulated patients free of biochemical progression, the median post-treatment PSA level was less than 0.1 ng/ml. When integrated across risk groups and ADT use, BMI had no statistically significant impact on biochemical progression-free survival.

Original Research Papers

Merrick GS *et al*. Impact of supplemental external beam radiotherapy and/or androgen deprivation therapy on biochemical outcome after permanent prostate brachytherapy. *Int J Radiat Oncol Biol Phys* 2005; **61**: 32–43.

Merrick GS *et al*. Influence of body mass index on biochemical outcome after permanent prostate brachytherapy. *Urology* 2005; **65**: 95–100.

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