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Contents

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BASIC SCIENCE: Epigenetics And Prostate Cancer - Heads Up! Epigenetics is the NEXT BIG THING in the unraveling of prostate cancer biology.

This article isn't an exposition of the molecular biology of epigenetics, e.g. promoter methylation, chromatin restructuring from histone modifications, histone deacetylase inhibitors, etc. But rather it is a concise alert to clinicians that developments in the understanding of the epigenetics of prostate cancer are beginning to provide insight into the inception and progression of the disease, improve estimates regarding prognosis, and, in the future, lead to new treatments.

"Epigenetics" refers to the study of heritable changes - acquired or inherited - in gene _expression independent of changes in the DNA sequence. Epigenetic (literally "above the genome") molecular mechanisms controlling gene expression are especially significant in the biology of cancer, involving "silencing" of tumor suppressors, and releasing undesirable constraints on the transcription, e.g. by unleashing restraints on cell-cycle regulators resulting in excessive proliferation. Throughout the course of the disease, from its inception through progression to androgen independent metastatic disease

prostate cancer displays increasing disruption of normal gene expression, especially resulting from aberrant methylation of gene promoter sequences. These alterations can be detected and quantified in core biopsy specimens, in the cellular sediments in urine, and in extra-cellular tumor DNA in peripheral blood plasma and serum.

The many snippets of epigenetic research peppering the current literature were joined in the comprehensive review, "The emerging roles of DNA methylation in the clinical management of prostate cancer" in Endocrine-Related Cancer (2006)13 by Perry et al. The article's lead sentence reads: "Prostate cancer has a unique set of problems with its early detection, diagnosis and treatment that might be aided by the complementary use of molecular markers such as DNA hypermethylation".

What are some of these areas where quantification of the DNA methylation status could be informative?

1) In diagnosis: by employing a panel of methylation markers for early detection. The putative progression of HGPIN to PCa is marked e.g. by increasing methylation of the GSTP1 gene (coding for a detoxification enzyme), for which a urine and serum test is in current clinical use. Also, "A four-gene panel of GSPT1, APC, PTGS2 and MDR1 [can] distinguish primary CaP from benign prostate tissue with 92% specificity and a sensitivity approaching 100%".
2) By utilizing promoter hypermethylation as a prognostic indicator for prostate cancer: "Several studies have now shown that the 'methylation index', defined as the ratio of methylated genes to the total number of genes analyzed, correlates with the clinicopathologic indicators of poor prognosis". Patterns of gene methylation -veritable "methylation signatures" are becoming associated with advancing pathologic stage and grade.
3) By identifying the silencing of genes that suppress metastases: methylation of genes for E-cadherin and CD44, both of which promote cell-cell adhesion, may serve as an alert to metastatic potential.

"DNA methylation alterations affects at least 30 genes. ...[and] These changes make prostate carcinoma particularly susceptible to drugs targeting chromatin and DNA modifications" (Schultz,'Epigenetics of prostate cancer: beyond methylation', J.Cell.Mol.Med., Oct.,2006). Since epigenetic alterations are potentially reversible, drugs to *reverse* the effects of unwanted methylation are under active development. Two 5-aza-cytidine compounds are in current clinical and protocol usage. Another class of drugs under investigation, the histone deacetylase (HDAC) inhibitors, prevent the removal from histone tails of the acetyl groups that maintain an open passageway for the transcription machinery to access DNA. "The administration of these drugs causes multiple changes as a consequence of demethylation, including activation of silenced genes, decondensation of chromatin and induction of cellular differentiation" (Perry).

On Friday, November 17th, at Swedish Hospital, the Annual Roland Pinkham Basic Science Lectureship is focusing on "Epigenetics: One Step Above the Genome" to promote clinicians' understanding of this developing science, a science which will likely pervade clinical medicine in the future. Addresses will discuss the underlying basic science, gene silencing, environmental and dietary effects on gene _expression, relevance of epigenetics to cancer, emerging directed therapies, and epigenetic factors affecting memory and aging. To register go the *www.swedish.org/cme* , or call 206-386-2755

DIAGNOSTICS: MODIFIED PSA GUIDELINES FOR BONE SCANNING

There is general consensus that at the ***initial diagnosis*** of prostate cancer the Technetium-99M bone scan has a low efficiency - about 1% - for detecting metastatic cancer when PSA values are less than 20 ng/mL. However, there is data that indicates that in presentations with Gleason scores ≥8 this level might better be lowered so that bone scanning may be safely avoided at PSA values of <10 ng/mL. An entirely different issue is what is the diagnostic efficiency of the Technetium scan in the diagnosis of bone metastases when the disease is ***recurrent*** ***after*** primary surgical or irradiation treatment?

This issue was addressed by Chodak, Iverson, McLeod et al. in J. Urol., July 2006: "Are Bone Scans Necessary in Men With Low Prostate Specific Antigen Levels Following Localized Therapy?". Their data base was the Early Prostate Cancer trial comparing treatment with bicalutamide (4052 men) to a placebo (4061 men) in men diagnosed with T1-4, MO and N+, N-, or Nx disease. Serial bone scans (a total of 10,389) were performed at approximately yearly intervals regardless of PSA levels. Results: "In the groups treated with radiation therapy or radical prostatectomy, regardless of the addition of bicalutamide, the incidence of positive bone scans was low (0.2% to 1.4%) at prostate specific antigen levels of less then 5 ng/mL". Specifically, for the placebo-treated RP group with PSA levels of <5 ng/mL only 15 of 2465 (0.6%) scans were positive. In the bicalutamide-treated post-RP group 5 of 2594 (0.2%) were positive. In the radiation therapy cohort receiving the placebo 9 of 643 (1.4%) showed positive scans, and in the bicalutamide treatment RT group 7 of 794 (0.9%) scans were positive at PSA level of < 5 ng/mL. A "watchful waiting" group was included in the trial and also received bicalutamide vs. placebo. In this cohort the positive bone scan rate for PSA values <5 ng/mL was 0.7% vs. 1.3%, respectively; and for PSA range 5 - 10 ng/mL, 2.3% vs. 2.2%; and for PSA range 10-20 ng/mL, 3.2% vs. 1.4% - for an overall positivity of less than 2%. The data from the "watchful waiting" group led the authors to conclude that the level below which a bone scan may be omitted "can be increased to 20 ng/mL with caution in those patients treated with watchful waiting".

This study deserves credibility since it is the largest of its kind addressing this issue, and in the authors' opinion "provides sufficient support for clinicians to eliminate routine bone scans in patients [after primary therapy] with PSA less than 5 ng/mL".

In the JCO, March 20,2005, article Kattan et al.,"Pattern of Prostate -Specific Antigen (PSA) Failure Dictates the Probability of a Positive Bone Scan in Patients With an Increasing PSA After Radical Prostatectomy", reported that the PSA level [as discussed above] and post-treatment PSAV were the only significant predictors of a positive scan. The median PSAV for positive scans was 1.4 ng/mL/mo vs. 0.12 ng/mL/mo for negative results. Based on their data a multi-parameter nomogram was constructed to predict the likelihood of a positive bone scan.

However, with the increasing use and increased specificity and sensitivity of the newer non-specific bone tracer, 18F-Fluoride, results from studies using Fluoride-18 PET/CT for skeletal evaluation will likely lead to revised parameters for bone scanning. Comparison analyses between the planar scan using the Technetium tracer and the F-18 PET/CT have shown that the F-18 radioisotope provides improved spacial resolution (to about 5-6 mm), and the associated CT offers more precise anatomic correlation and structural detail. The current combination of the two in a single procedure offers a more confident differentiation between benign and malignant lesions. It is very likely that a lower value will be established for the PSA level at which scanning provides informative results. In a 2006 review of the new tracers for scanning in Seminars in Nuclear Medicine, Langsteger et al, conclude "Therefore, in high risk patients (GsC >7 or PSA doubling time < 3 months) we recommend 18F-fluoride PET/CT and not BS as the primary staging procedure".

It is possible that even further changes are afoot in bone scanning technique. Dr. David Djang, Seattle Nuclear Medicine, commented, "The anatomy is so good with the F-18 PET that I feel adding the CT gains nothing or extremely little for anatomical localization. There are some lytic lesion that will show better on CT, but this is hardly ever the case with the blastic lesions of prostate cancer. With F-18 PET's greater accuracy compared to traditional bone scans, I suggest that far fewer MRIs would be necessary for confirmation/exclusion of disease, and omitting the CT would save the system money."

DIAGNOSTICS: National Comprehensive Cancer Network (Nccn) Establishes 2006 Guidelines For Early Detection Of Prostate Cancer.

In May, 2006, on the recommendation of its panel of prostate cancer experts the NCCN published a revision of the professional practice guidelines for PSA screening. The new recommendation is that a biopsy should now be considered for DRE negative men with PSA ≥2.6 ng/mL. *or* a PSA velocity of >0.5 ng/mL/yr when the PSA is < 2.5 ng/mL. This information is found on the NCCN.org web site in the prostate cancer section of "Guidelines for Detection, Prevention, and Risk Reduction" on screen PROS D5. Reference is made to the addition of %free PSA in the decision as to whether to perform a biopsy, and they suggest that for %free PSA ≤ 10 - perform biopsy; for %free PSA 10-25 - consider a biopsy; and when the free PSA is > 25% - no biopsy. In the footnote section additional comments include: 1) "For men with PSA < 4 ng/mL, data suggest that a PSA velocity of >0.5 ng/mL/yr is suspicious for the presence of cancer, and a biopsy is recommended; 2) "for men with PSA 4-10 ng/mL a PSA velocity of >0.75 ng/mL/yr is suspicious for cancer"; 3) "Measurement should be made on at least three consecutive specimens drawn over at least an 18-24 mo. interval"; and lastly, "The same assay should be used" [and] ... "biologic variability may be a confounding factor in determining PSA velocity". Other factors affecting the biopsy decision are "patient's age, co-morbidity, %free PSA, prostate exam/size, strength of family history, African American".

The lower PSA threshold of >2.5 ng/mL will certainly lead to more biopsies and an increased rate of prostate cancer diagnosis, but will not avoid the stubborn problem of the PSA test's low specificity. The Prostate Cancer Prevention Trial found that for men with a normal DRE and PSA level between 2.1 - 3.0 ng/mL the incidence of cancer was ~21%; and was ~24% in the PSA range of 3.1-4.0 ng/mL. Urologists are well aware that more than 70% of biopsies based only on the PSA value will be negative.

PSA Velocity and age-adjusted PSA ranges each individually can add useful nuance in PSA interpretation. In his Abstract #1, 2006 Prostate Cancer Symposium, Dr. Judd Moul (recently elected to serve on the NCCN prostate cancer panel of experts) presented a study *combining* the two and created "age-normalized PSA velocity" thresholds to guide the decision of whom to biopsy. "PSAV was calculated and its percentiles were normalized to ages 40-59, 60-69, and > 70 as well as PCa status." Statistical considerations indicated that optimal PCa detection would result if biopsies were performed if the PSAV exceeded 0.25 ng/mL/yr in men 40 - 59; 0.05 ng/mL/yr for 60-69; and 0.75 ng/mL/yr in men older than 70 years. By using these thresholds in evaluating the biopsy outcome of 11,347 men with PSA values < 4.0 ng/mL the cancer detection rate in the age group 40-49 years was 35% and was 57% in the 60-69 year old cohort, compared to the detection rate of 19% and 25% using the "traditional standard (0.75 ng/mL for all age groups)." Dr. Moul et al. concluded that the use of these *age-normalized PSAV thresholds* "could substantially improve PCa detection".

CLINICAL BRIEFS:

DIAGNOSTICS: "Defining Biochemical Recurrence of Prostate Cancer After Radical Prostatectomy: A Proposal for a Standardized Definition", JCO, August 2006. Scardino et al. argue that a PSA value of "at least 0.4 ng/mL followed by another increase best explained metastatic progression". The analysis controlled for clinical variables and was based on follow-up of 3125 men post-RP. Ten candidate definitions of recurrence were considered among which the 10-year progression-free probability ranged from 63% to 79%.

DIAGNOSTICS: "Clinical usefulness of serum prostate specific antigen for the detection of prostate cancer is preserved in men receiving the dual 5alpha-reductase inhibitor dutasteride [0.5 mg/d]", J.Urol. May 2006. It has been reasonable to assume that, just as for finasteride, the PSA value should be doubled during dutasteride treatment. Andriole et al. from a study of 2802 >50 year old cancer free men with BPH and PSA values ranging from 1.5 - 10 ng/mL concluded, "A doubling factor is effective for maintaining the sensitivity and specificity for detection of prostate cancer in men on dutasteride".

PREDICTING OUTCOME OF PRIMARY Tx: "Comparison of high-dose proton radiation therapy vs. brachytherapy in localized prostate cancer: A case-matched analysis", Abstract #38, 2006 Prostate Cancer Symposium. Shipley, Zietman et al. based their conclusion on a comparison between 132 men (T1-2, PSA $\leq$ 15) receiving high dose EBRT (79.2 Gy) in trial PROG 95-09 with 132 carefully matched men treated with brachytherapy at MGH: "High dose EBRT is equivalent to brachytherapy for control of localized [low- and intermediate-risk] prostate cancer". 5-year results: OS and metastases free survival was 98% for both groups; bNED 88% and 90% for EBRT and brachytherapy, respectively.

HORMONAL INTERVENTION: "Deferred combined androgen blockage therapy using bicaultamide [80mg/d] in patients with hormone-refractory prostate cancer during androgen deprivation monotherapy", BJU-Int, June 2006, Tokyo Medical University. The study followed 44 patients, high-risk at diagnosis, with metastatic prostate cancer who had developed HRPC (based on three consecutive rises in PSA to a median of 9.6 ng/mL) during first-line androgen deprivation therapy. At the time of PSA relapse, bicalutamide 80 mg/d was administered. A $\geq$ 50% decline in PSA was seen in 29 men (66%) who then experienced a median PSA failure-free survival of an additional 9.2 months. The Gleason score predicted the likelihood of failure-free survival (FFS): for men with Gleason 6 or 7 the median FFS was 13 months, and for Gleason 8-10 the median FFS was 4 months. The PSA-DT on bicalutamide was also predictive of PSA FFS. For men with PSA-DT of >4 months the 1- and 2-year FFS rates were 43% and 31%, while for PSA-DT of < 4 months 21% were free of PSA progression at 1 year and none at 2 years. The median overall survival *from the start of ADT monotherapy* for those who responded to bicalutamide had not been reached by 8 years, while for non-responders the median interval was 40 months.

ADJUVANT AND SALVAGE TX: "Immediate versus deferred androgen deprivation treatment in patients with node-positive prostate cancer after radical prostatectomy and pelvic lymphadenectomy", Lancet Oncol, 2006, July. This report by Messing et al. presents the final data analysis of the "Messing" trial ECOG EST 3886, first published in NEJM in 1999. Ninety eight men, clinical stage T2, were randomized to immediate/continuous ADT or ADT when *metastatic* disease was detected. Overall survival at median F/U of 11.9 years: immediate ADT 13.9 yrs. vs. 11.3 yrs. (P=0.04)

ANDROGEN INSENSITIVE DISEASE: Latest Report Of 'Accent': Docetaxel And Calcitriol

EXECUTIVE SUMMARY of what was reported at the Prostate Cancer Update Conference, Vail Colorado, February 2006: The Phase II ASCENT trial compared doxetaxel/placebo (D+P) with

docetaxel/calcitriol (D+C) in 250 men with progressive metastatic AIPC. The D/C combination showed a significant survival benefit compared to monotherapy. The recipe: catcitriol 45 *mcg* orally day 1, followed on day 2 by 36 mg/m2 docetaxel, both repeated weekly for a total of 3 consecutive weeks in a 4-week cycle. Oral Decadron, 4 mg, was given 1 hour before and 12 hours after chemotherapy. Results: PSA response (> 50% reduction) for those men on study for 6 months - D+P, 49%, D+C, 58%.
Overall PSA response for D+P vs. D+C: 52% vs 63%; median time in days to PSA response, 163 vs 87; measurable tumor response, 20% (n=56) vs. 28% (n=46), respectively. The estimated median survival for D+P was 16.4 months vs. 24.5 months for D+C. For D+P vs. D+C: neutropenia - 8% vs. 10%; fatigue - 16% vs. 8%; infection - 13% vs. 8%; hyperglycemia - 12% vs 6%, and for thromboembolic events 8.8% vs. 1.6%, respectively. Overall grade 3/4 toxicity was less in the D+C arm: 58% vs. 70%. A confirmatory ASCENT II is ongoing comparing the weekly regimen of the first trial with docetaxel at 75 mg/m2 q 3 weeks + prednisone 5 mg bid.

Why calcitriol, the active and most potent form of Vitamin D? As the ligand targeting the vitamin D receptor, calcitriol is potently antiproliferative and proapoptotic and exhibits synergy with chemotherapy.