PROSTA-GEN DX™
A NEW Biopsy-based tool for prostate cancer management

Examines two major mechanisms of carcinogenesis

P-TEN
LOSS OF TUMOR SUPPRESSOR GENE

TMPRSS2:ERG
GENE FUSION/TRANSLOCATION ANEUPLOIDY
Two studies show that the common recurrent gene fusion between TMPRSS2 and ERG promotes prostate cancer in both mouse and humans when PTEN is concurrently lost. In human prostate cancer, the presence of both these aberrations may be indicative of poor prognosis, suggesting that preclinical therapeutic research should target both of these pathways.

Recommendations over screening for early diagnosis of prostate cancer have recently gained attention, with increasing concern that the introduction of routine prostate-specific antigen (PSA) blood testing has led to significant overtreatment of prostate cancer. This debate highlights the need to better understand the primary molecular determinants that drive prostate cancer.

Two papers on pages 524 and 619 of this issue now draw attention to a close collaboration between ETS transcription factors and the PTEN tumor suppressor, which together seem to be pivotal in both human and murine prostate cancer.

Proteins of the ETS family are a group of related signal-dependent transcriptional regulators mediating cellular proliferation, differentiation and tumorigenesis. In human prostate cancer, genomic alterations of ETS-related genes (principally ERG) as a result of a fusion between an androgen receptor–regulated gene promoter of TMPRSS2 and ETS transcription factors is present in about half of tumors. Given this high frequency of ETS genetic rearrangements in prostate cancer, it is plausible that overexpression of ETS factors per se may represent a crucial event in prostate tumorigenesis. However, important details of the biological role of aberrant ETS expression in prostate cancer initiation and progression need to be clarified.

Since this discovery was made, there has been considerable interest in understanding the mechanism by which the TMPRSS2-ERG fusion may promote progression to prostate cancer. Studies have used various mouse models that often take advantage of the probasin promoter to drive prostate-specific expression of the TMPRSS2-ERG transgene. An early indication that the initial steps of cancer have been triggered in the mouse is when a transgene elicits the formation of benign prostatic intraepithelial neoplasia (PIN) in the prostate gland. In human disease, the presence of high-grade PIN is strongly associated with the development of cancer. However, deriving a precise morphological definition of PIN that can be identified in different mouse models can be problematic, and this has led to various interpretations concerning the stage in the disease process that TMPRSS2-ERG activation leads to cancer.

Concurrent loss of PTEN

The two reports in this issue now demonstrate that the role of the PTEN pathway is crucial in understanding the interplay between TMPRSS2-ERG activation, PIN and prostate cancer oncogenesis.

PTEN is among the most commonly mutated tumor suppressor genes in human cancer, and like many other tumor suppressors, PTEN targets proteins in signaling pathways that regulate cell growth and survival and contributes to cancer when lost or inactivated. Mouse models have shown that Pten-deficient mice develop high-grade PIN, but without progression to prostate cancer.
ONLY TECHNOLOGY THAT COMBINES HISTOLOGIC, MOLECULAR AND CLINICAL PARAMETERS TO PREDICT DISEASE PROGRESSION

HISTOLOGIC

• Quantitatively captures and analyzes cellular features

• Pathologist selects the most representative tumor area for analysis

MOLECULAR

• Fluorescent in-situ hybridization captures loss or translocation of gene.

• Computer digital imaging quantifies and captures biologic results.

CLINICAL

• Incorporates clinical features to complete patient analysis.

• Biopsy Gleason Score
The PTEN (phosphatase and tensin) gene encodes a phosphatase which counteracts the PI3K/Akt signaling pathway, one of the most critical cancer-promoting pathways identified to date. It is involved in the regulation of DNA repair, genomic instability, stem cell self-renewal, cellular senescence, and cell migration (metastasis).

Studies published correlate PTEN deletion with poor clinical outcome in cases of hormone refractory prostate cancer, with 42.6% of tumors displaying the PTEN deletion. In addition, it has been observed that the frequency and type of PTEN deletion is correlated to disease progression and early biochemical recurrence.
TMPRSS2-ERG gene rearrangements are present in 30-50% of prostate cancer and lead to over expression of a truncated ERG protein. The presence of the rearrangement may have prognostic significance and assist in patient stratification to guide therapy.

Hormonally treated PCA patients having an ERG rearrangement have a significantly increased risk of becoming castration resistant compared to patients without the rearrangement. This is a sign of more aggressive disease and could potentially be used to identify patients less likely to respond to hormone treatment.
At diagnosis

We have used multiple scientific disciplines to predict disease progression at the time of diagnosis.

• Two major mechanisms of carcinogenesis are examined.

• Generates a personalized prediction of risk of disease progression.

• Determines patients’ genetic prognosis for serious disease progression.

• Delivers clinically proven, reliable results.

• Provides physicians and patients with enhance insights for treatment decisions.


