Cancers can house selected genetic mutations that promote or slow tumor development. Researchers work to unearth recurrent mutations because they may pinpoint casual cancer genes or molecular subtypes with prognostic or predictive significance. Recurrent mutations in a handful of genes have been implicated in prostate cancer (PCa) development and progression. But until recently, causal events were unknown for the majority of PCa cases and well-defined molecular subtypes had not been described. Here, I describe the discovery of recurrent ETS gene fusions in PCAs and their roles in molecular subtyping and patient management.

We developed a bioinformatics algorithm (COPA) to analyze expression-profiling data in order to prioritize “outlier” genes that show overexpression in only a subset of cancer cases (1). When applied to Oncomine—a database of human cancer microarray data—COPA correctly identified outlier genes in specific cancer types with known recurrent genetic aberrations, such as ERBB2 in breast cancer.

**LETS GET TOGETHER**

In multiple human PCa data sets, COPA identified strong outlier profiles for ERG (ETS-related gene) and ETV1 (ETS variant 1), two genes that encode ETS family transcription factors and are involved in recurrent rearrangements in blood and soft tissue cancers. Characterization of human PCa tissues with outlier expression of ERG or ETV1 identified fusions of these genes with the 5′ untranslated region of the prostate-specific, androgen-induced TMPRSS2 gene (1). These fusions existed only in PCa tissues that overexpressed one of the two ETS family genes and were not detected in benign prostate tissues. Fluorescence in situ hybridization (FISH) revealed ETS gene rearrangements in 50 to 75% of PCAs from prostate-specific antigen (PSA)–screened Caucasian populations. Analysis of PCa cell lines revealed that the TMPRSS2:ERG fusion conferred androgen-regulated ERG gene expression. Thus, the androgen-responsive elements that normally restrict TMPRSS2 expression to the prostate drive aberrant ETS oncogene overexpression in TMPRSS2:ERG+ PCa. PCa tissues have subsequently been found to contain distinct rearrangements between ETS family genes and other 5′ fusion partners that specify either androgen-driven or constitutive gene expression (2).

**MEETING MEDICAL NEEDS**

The ultimate goal of identifying cancer-driving genetic alterations and defining disease subtypes is improvement in clinical medicine. ETS fusions are robust candidates for diagnostic-test development, early-detection markers, and molecular subtyping for precision medicine.

Given the PCa specificity of ETS gene fusions, their detection in tissues may be useful in diagnosis. Although FISH can be used to detect ETS gene fusions, the assays can be challenging to perform and interpret in clinical laboratories. However, the most common ETS fusion in PCa, TMPRSS2:ERG, encodes a nearly full-length version of the ERG transcription factor. Recently, monoclonal antibodies (mAbs) have been raised against ERG, and immunohistochemistry (IHC) experiments performed with these mAbs in PCa tissues show high concordance with the FISH experiments (3). In prostatectomy specimens, ERG expression is rare; if ever, detected in benign glands. Evaluation of ERG staining in needle biopsy specimens confirmed the cancer-specificity of ERG expression, and IHC for ERG is now being used for diagnostically challenging PCa cases (3, 4).

We have also investigated the use of ETS fusions as early-detection biomarkers. The TMPRSS2:ERG gene fusion product is not secreted, limiting the utility of serum-based detection. However, TMPRSS2:ERG transcripts are detectable and quantifiable in post–digital rectal exam (DRE) urine, similar to PCA3, a noncoding PCa biomarker. In collaboration with the manufacturer of a urine-based PCA3 assay, we developed and evaluated a clinical-grade assay to quantify TMPRSS2:ERG in post-DRE urine. In a multi-institution study of >1300 men, urine TMPRSS2:ERG was significantly associated with the presence of cancer in tissues from biopsy and prostatectomy (5). Urine TMPRSS2:ERG and PCA3 measurements improve the performance of serum PSA assays and multivariate models for predicting cancer with biopsy (5). Furthermore, evaluation of urine TMPRSS2:ERG in prostatectomy patients who had all tumor foci tested for ERG by IHC revealed that ~80% of prostate harbor at least one ERG+ cancer focus and that urine TMPRSS2:ERG and total ERG+ cancer burden are highly correlated (6). The combined urine TMPRSS2:ERG and PCA3 assays should be available to patients in the immediate future.

**PRECISION MEDICINE**

ETS-fusion positive (ETS+) and negative (ETS−) PCas have distinct expression profiles, suggesting that they represent fundamentally different disease subtypes (Fig. 1). What lesions drive ETS+ PCa? Using computational and experimental approaches, we identified SPINK1 outlier expression in ~10% of PCas, which were exclusively ETS+, and demonstrated that SPINK1 drives PCa phenotypes using in vitro and in vivo models (7).

To move beyond simple ETS–based stratification for precision medicine in advanced PCa, we recently performed an integrative exome sequencing–based study of 11 aggressive, localized PCas and 50 lethal, metastatic castration-resistant prostate cancers (CRPCs) (8). This study provided insight into commonly mutated genes and pathways and identified recurrent disruptions of CHD1 as defining a previously unidentified subset of ETS+ PCa. ETS fusions, which were present in 50% of CRPCs, were markedly overexpressed in the vast majority, which is consistent with persistent androgen signaling in CRPC and the observed clinical benefit of antiandrogenic therapy in that setting.

The discovery of ETS fusions represents a paradigm shift in our understanding of the types of mutations that drive common epithelial cancers, which are responsible for most cancer mortality. Disease-driver gene fusions have since been identified in other carcinomas, such as EML4:ALK in lung cancer. ETS fusions have provided insight into...
PCa biology, are the basis for robust molecular subtyping (9, 10), and are being exploited for both PCa diagnosis and early detection. In fact, ETS status is being evaluated as part of the first biomarker-directed PCa clinical trial (NCT01576172). The ETS saga in PCa demonstrates how comprehensive evaluation of cancer genomes and transcriptomes can inform disease biology and enhance the clinical management of cancer patients.

REFERENCES AND NOTES


Competing interests: I have received consulting honoraria from Ventana Medical Systems/Roche (VMS), am co-inventor on U.S. patents 7,718,369 and 8,211,645 (on ETS fusions in PCa), and submitted patents on SPINK1 in PCa, which were issued to the University of Michigan. Diagnostic rights have been licensed to Hologic/Gen-Probe, who has sublicensed some rights to VMS.

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