**Supplementary Methods.**

**Histologic, immunohistochemical, and FISH analyses**

In the narrative, the term “PDXs” will be inclusive of MDA PCa 2a-T and 2b-Txenografts (T stands for cell line–derived xenografts).

Subcutaneous tumor samples of PDXs are fixed in 10% neutral buffered formalin and embedded in paraffin. Serial 5-µm-thick tissue sections are cut from each sample; one section is used for H&E staining, and adjacent sections are used for immunostaining and/or FISH analysis as described below.

Human prostate cancer (PCa) tissue samples utilized for immunohistochemical stains and molecular studies were obtained from the PCa tissue bank supported in part by the Prostate Cancer Specialized Program of Research Excellence at MD Anderson Cancer Center. All sections were from formalin-fixed, paraffin-embedded tissue specimens. Sections derived from bone metastases were decalcified in formic acid (1, 2).

For the neuroendocrine classification of tumors, we followed current clinical pathology practice, namely, immunohistochemical positivity for either synaptophysin (SNP), chromogranin A (CGA), or CD56 (NCAM) (3, 4). Although adenocarcinomas can express neuroendocrine markers, we follow the recommendation by the Prostate Cancer Foundation assembled working committee (3) not to perform immunohistochemical analyses for neuroendocrine markers in otherwise morphologically typical adenocarcinoma.

Immunohistochemical studies outlined in Table 1, Fig 1, and Fig S1 were performed at the immunohistochemistry laboratory (Division of Pathology and Laboratory Medicine, MD Anderson Cancer Center) using the Leica Bond III automated immunohistochemical stainer following standard procedures (Leica Biosystems, Buffalo Grove, IL, USA). AR: monoclonal antibody, clone AR441 (Dako, Carpinteria, CA, USA). CD56: monoclonal antibody, clone 123C3 (Leica Biosystems). Chromogranin A: monoclonal antibody, clone LK2H10 (ED Millipore, Burlington, Massachusetts, USA). Synaptophysin: monoclonal antibody, clone 27G12 (Novocastra, Newcastle upon Tyne, United Kingdom). Immunohistochemical staining results were evaluated by the study pathologists ELT and PT.

Immunohistochemical and RNA-ISH analyses listed in Table S2 and Fig 2 were performed in the laboratory of Dr. Arul Chinnaiyan following the methods described previously (5, 6). Briefly, ERG-PTEN dual immunohistochemisty was performed using anti-ERG (EPR3864) rabbit monoclonal primary antibody (1:100) (Cat#790-4576, Ventana Medical Systems, Inc., Tucson, AZ, USA) and a rabbit monoclonal primary antibody against PTEN (1:25) (138G6, Cell Signaling Technology, USA). Dual immunohistochemistry was performed using an automated protocol developed for the Discovery XT automated slide staining system (Ventana Medical Systems, Inc.) using Ultramap anti-rabbit HRP (Ventana Medical Systems, Inc.) for ERG and Ultramap anti-rabbit AP (Ventana Medical Systems, Inc.) for PTEN as secondary antibodies. Detection of ERG and PTEN signal was performed using ChromoMap DAB (Ventana Medical Systems, Inc.) and ChromoMap Blue (Ventana Medical Systems, Inc.) respectively. Nuclear Fast Red counterstain (Ventana Medical Systems, Inc.) was used as the counterstain. ERG-PTEN immunohistochemical staining was evaluated by the study pathologist LPK.

AR immunohistochemistry was performed using a mouse monoclonal antibody against AR (Clone AR441, Thermo Scientific, USA) (1:50) as described above using the automated protocol for the Discovery XT staining system (Ventana/Roche). ERG, AR, and SPINK1 immunohistochemical staining was evaluated by pathologist LPK.

Immunohistochemical analyses outlined in Fig 3 were performed in the laboratory of Dr. Nora Navone following the methods described previously(7).

**Immunohistochemistry evaluation criteria**

ERG staining was evaluated by the study pathologist LPK. Staining of vessels with nuclear expression was used as a positive control. Cores not displaying staining of vessels were categorized into the “antibody did not work” group. In addition, we used PCa samples with known *ERG* rearrangement (confirmed by FISH) as a positive control.

We defined staining as positive for PTEN when the majority of cells (> 90%) showed PTEN staining. Staining was defined as negative (deletion) when it was either absent or weak in < 10% of cells. When 50% of cells express PTEN, it was defined as heterogeneous deletion. PTEN immunohistochemistry results were further validated by simultaneous FISH studies on the tissue microarrays.

**Fluorescence *in situ* hybridization (FISH)**

BAC clones were used to generate the dual-color, break-apart FISH probes. All clones were tested on normal chromosomes for the confirmation of map position and have been used extensively in various studies from our laboratory and from others (8, 9).

**BAC DNA Preparation**

Midiprep method: 200 mL overnight cultures for each BAC clone were grown in LB medium containing 12.5 μg/mL of chloramphenicol and incubated at 37°C for 14 to 16 hours with constant shaking. DNA was prepared using Qiagen midiprep kit using Qiatip-100 according to manufacturer’s instructions.

**Probe labeling**

All the probes were prepared by nick translation labeling using modified nucleotides conjugated with biotin or digoxigenin using biotin nick translation mix (Roche-11745824910) and digoxigenin nick translation mix (Roche-11745816910) for the 3’ and 5’ probes, respectively. Probe DNA was precipitated and dissolved in hybridization mixture containing 50% formamide, 2XSSC, 10% dextran sulphate, and 1% Denhardt’s solution. Approximately 200 ng of each labeled probe was used for hybridization. Fluorescent signals were detected with Streptavidin Alexa Fluor 594 (Invitrogen) and anti-digoxigenin-fluorescein Fab fragments (Roche-11207741910) that produce red and green signals, respectively.

**Image capture and FISH signal analysis**

FISH scoring was performed by an experienced cytogeneticist (NP) and a pathologist (WY). Samples displaying aberrant signal patterns in more than 10% to 15% of cells were designated “abnormal,” a cut off established for needle biopsy samples. Fluorescent images were captured using a high-resolution CCD camera controlled by ISIS image processing software (Metasystems, Germany).

**Real-time RT-PCR**

Expression of human FGFRs by real-time RT-PCR was assessed using human-specific primers following procedures described previously(7). Human-specific primers for FGFR1, 3, and 4 were previously reported (7). For FGFR2 we used the following primers: FGFR2R (TGCAGACAAACTCTACGTCT) and FGFR2F (CGT ACC ACC TGG ATG TTG TG).

**Array comparative genomic hybridization**

Array comparative genomic hybridization (aCGH) was performed on a panel of 37 PDXs using Agilent 1M Human Genome Microarrays (Agilent Technologies, Santa Clara, CA). Below are listed the passage numbers (P) of the PDXs used to performed aCGH: MDA PCa 2b-T (P5), MDA PCa 43 (P2), MDA PCa 79 (P2), MDA PCa 86 (2), MDA PCa 91B (3), MDA PCa 94 (1), MDA PCa 100-C6 (2), MDA PCa 101 (2), MDA PCa 108 (2), MDA PCa 112 (2), MDA PCa 115-C1 (P3), MDA PCa 117-9 (2), MDA PCa 137-13 (P2), MDA PCa 144-4 (P2), MDA PCa 144-13 (P2), MDA PCa 146-10 (P2), MDA PCa 146-12 (P2), MDA PCa 146-20 (P2), MDA PCa 149-1 (P1), MDA PCa 150-1 (P2), MDA PCa 150-3 (P2), MDA PCa 152-1 (P2), MDA PCa 153-7 (P2), MDA PCa 153-14 (P1), MDA PCa 155-12 (P2), MDA PCa 155-16 (P2), MDA PCa 160-29 (P2), MDA PCa 166-1 (P2), MDA PCa 170-4 (P2), MDA PCa 175-2 (P2), MDA PCa 175-6 (P3), MDA PCa 175-10 (P2), MDA PCa 177-B (P2), MDA PCa 180-11 (P2), MDA PCa 180-30 (P3), MDA PCa 183-A (P3), MDA PCa 188 (P2).

Sample labeling and hybridizations were performed according to the manufacturer's instructions. Human spleen DNA was used as a normal reference in each hybridization. Tumor and control genomic DNAs were labeled with Cy3-dUTP and Cy5-dUTP, respectively. Hybridized slides were scanned on an Agilent DNA Microarray Scanner (Agilent Technologies), and images were extracted using Agilent Feature Extraction software. The aCGH data were analyzed using Agilent Genomic Workbench (v.5.0.14), using a *Z*-score algorithm with a threshold of 2.0 and a 1 pt window to identify breakpoints and at 50 pt for copy number changes.

**RNA sequencing**

RNA sequencing was performed following previously established protocols (7). For this study we used MDA PCa 144-4 (P3), MDA PCa 144-13 (P2), MDA PCa 146-10 (P2), and MDA PCa 146-12 (P1).

**ETV1 RNA *in situ* hybridization.**

ETV1 RNA-ISH analysis on MDA PCa 177 was carried out as described previously (6).

**Bioinformatic analysis**

For differential expression analysis, significant genes are defined using FDR 0.01 and a fold change of 2. Relative enrichment of genes sets and pathways in MDA PCa 144 and MDA PCa 146 pairs was assessed by gene set enrichment analysis (10). Genes enriched in MDA PCa 144-13 (vs MDA PCa 144-4) would be “positive correlated,” and genes enriched in MDA PCa 146-10 (vs MDA PCa 146-12) would be “positive correlated.” Hallmark pathway databases were used.

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