**Supplemental Table S1. Primer sequences for qRT-PCRs.**

| Primers | Sequences |
|---|---|
| **STAT2-F** | GAGGCCTCAACTCAGACCAG |
| **STAT2-R** | GCGTCCATCATTCCAGAGAT |
| **STAT1-F** | CCGTTTTCATGACCTCCTGT |
| **STAT1-R** | TGAATATTCCCCGACTGAGC |
| **RHOU-F** | AGGCCTCTCTGCTACACCAA |
| **RHOU-R** | TCAGGCACTGGCTTTTCTTT |
| **RHOA-F** | AAGGACCAGTTCCCAGAGGT |
| **RHOA-R** | TTCTGGGGTCCACTTTTCTG |
| **PIK3CB-F** | TCAGCCTTCGCTCCTAATGT |
| **PIK3CB-R** | TGCAAAGTCAGCAGGAAATG |
| **MAPKAPK2-F** | GAGCCCTCAGACATCTCCAG |
| **MAPKAPK2-R** | CCAAGAAGGGAGAAGGTTCC |
| **ITGB5-F** | ACAAGGGAGTCCTCTGCTCA |
| **ITGB5-R** | GGGGCACTTCTCACACATCT |
| **GIT1-F** | CCATGGACGTGTATGACGAG |
| **GIT1-R** | GCAAACTCTCGGGCATTAAA |
| **FGF13-F** | GGGTGGTATCTGGGTCTGAA |
| **FGF13-R** | CATTGTGGCTCATGGATTTG |
| **EIF3B-F** | GCCTCCTGCAGAAGAACAAC |
| **EIF3B-R** | CTTCCGGAAATCTTCCATCA |
| **CSNIK2A1-F** | ATCTTTCGGAAGGAGCCATT |
| **CSNIK2A1-R** | TATCGCAGCAGTTTGTCCAG |

| Primers | Sequences |
|---|---|
| **KLK3-F** | CGGAGAGCTGTGTCACCAT |
| **KLK3-R** | GTGGGCAGCTGTGAGGAC |
| **ARA55-F** | GCTAGATCGGTTGCTTCAGG |
| **ARA55-R** | GCGGAAGTCAGAGAGTGAGG |
| **GNAO1-F** | GTGATGTGGTGAGTCGGATG |
| **GNAO1-R** | TACGATGCCAGTGGTTTTGA |
| **PRKCE-F** | GATGCAGAAGGTCACTGCAA |
| **PRKCE-R** | GTCGTCATGGAGGATGGACT |
| **PRKD1-F** | ACGGCACTATTGGAGATTGG |
| **PRKD1-R** | TGACCACATTTTCTCCCACA |
| **CALR-F** | TCTCAGTTCCGGCAAGTTCT |
| **CALR-R** | TCTGAGTCTCCGTGCATGTC |
| **TBP-F** | CAGCGTGACTGTGAGTTGCT |
| **TBP-R** | TGGTTCATGGGGAAAAACAT |
| **EIF1AX-F** | GTACTGGAGAGGGGAGAGCA |
| **EIF1AX-R** | TGAAGCTGAGACAAGCAGGA |
| **PPA1-F** | GGCTGTTGTGGTGACAATGA |
| **PPA1-R** | TGACTTTCCAGTCGGTTTCC |

**Supplemental Table S2. Primer sequences for ChIP-PCR validation of AR target genes.**

| AR Target Genes | Primers | Sequences |
|---|---|---|
| ***STAT1*** | Prom-STAT1-F | tctcacaagaggctggaggt |
| | Prom-STAT1-R | cagaaggaacgtgggagaag |
| ***RHOA*** | Prom-RHOA-F | gggattgtgcagagtggaat |
| | Prom-RHOA-R | catttcccttcgtggtgagt |
| ***PIK3CB*** | Prom-PIK3CB-F | gggcaacagtagcgaaactc |
| | Prom-PIK3CB-R | aaccgcgaaaaatcacagtc |
| ***MAPKAPK2*** | Prom-MAPKAPK2-F | tatgcagctcctttgacacg |
| | Prom-MAPKAPK2-R | cgtcacagcctcgtctgc |
| ***ITGB5*** | Prom-ITGB5-F | ttggccagtctcaaatcctt |
| | Prom-ITGB5-R | aaggttcctccaccttagcc |
| ***CSNK2A1*** | Prom-CSNK2A1-F | cccagaatgcttggctctac |
| | Prom-CSNK2A1-R | ccatgctgggatgtcctatt |
| ***KLK3*** | Prom-KLK3-F | tgggacaacttgcaaacctg |
| | Prom-KLK3-R | ccagagtaggtctgttttcaa |
| ***ACTB*** | ACTB-F | tgcccatctacgaggggtat |
| | ACTB-R | atgccagggtacatggtggt |

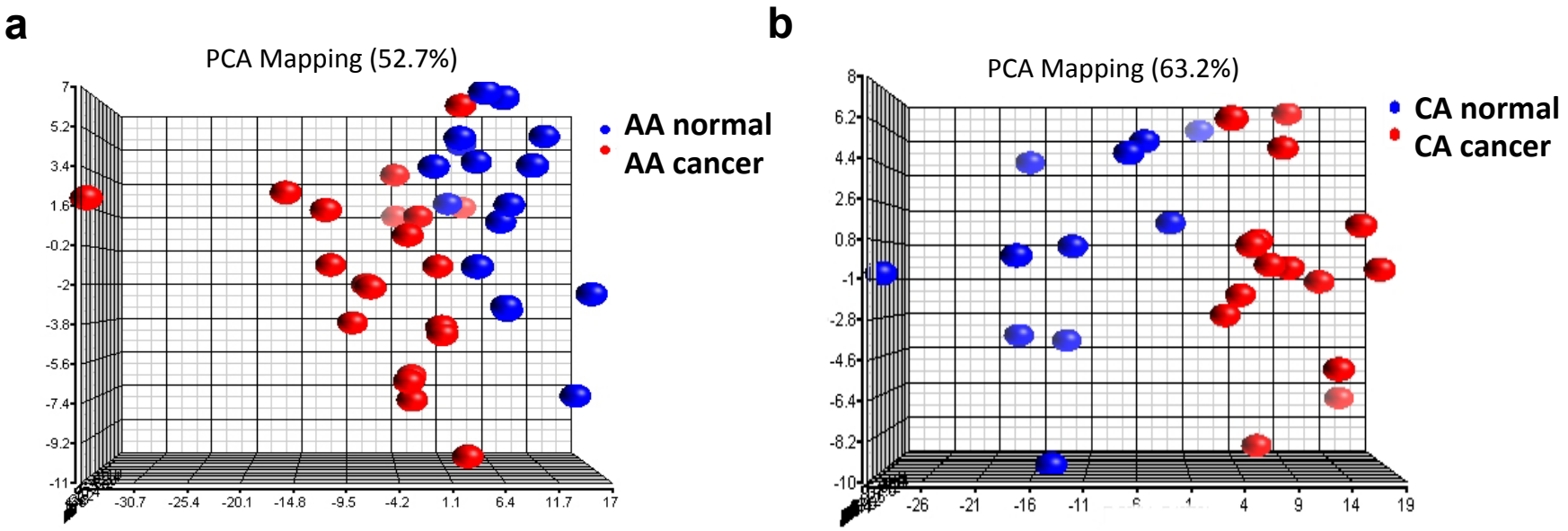
**Supplemental Table S4. Ingenuity canonical pathways that were significantly over-represented in AA cancer but not significantly over-represented in CA cancer.**

| Ingenuity Canonical Pathways | p-value |
|---|---|
| PI3K Signaling in B Lymphocytes | 0.000630957 |
| VDR/RXR Activation | 0.002511886 |
| Glutathione-mediated Detoxification | 0.002951209 |
| Prostanoid Biosynthesis | 0.006025596 |
| Signaling by Rho Family GTPases | 0.006456542 |
| tRNA Splicing | 0.008317638 |
| RhoGDI Signaling | 0.010715193 |
| Biotin-carboxyl Carrier Protein Assembly | 0.011220185 |
| Pyrimidine Ribonucleotides Interconversion | 0.012589254 |
| TNFR1 Signaling | 0.017782794 |
| Protein Kinase A Signaling | 0.019054607 |
| D-myo-inositol (1,4,5)-Trisphosphate Biosynthesis | 0.023442288 |
| UDP-N-acetyl-D-glucosamine Biosynthesis II | 0.02630268 |
| TNFR2 Signaling | 0.033884416 |
| TR/RXR Activation | 0.034673685 |
| Endoplasmic Reticulum Stress Pathway | 0.043651583 |
| Aldosterone Signaling in Epithelial Cells | 0.043651583 |
| Acetyl-CoA Biosynthesis III (from Citrate) | 0.044668359 |
| UDP-N-acetyl-D-galactosamine Biosynthesis II | 0.046773514 |
| Androgen Signaling | 0.048621521 |
| Lipid Antigen Presentation by CD1 | 0.049118723 |

**Supplemental Table S6. IPA canonical signaling pathways with over-represented AR target genes in the comparison of AA PCa versus CA PCa.**

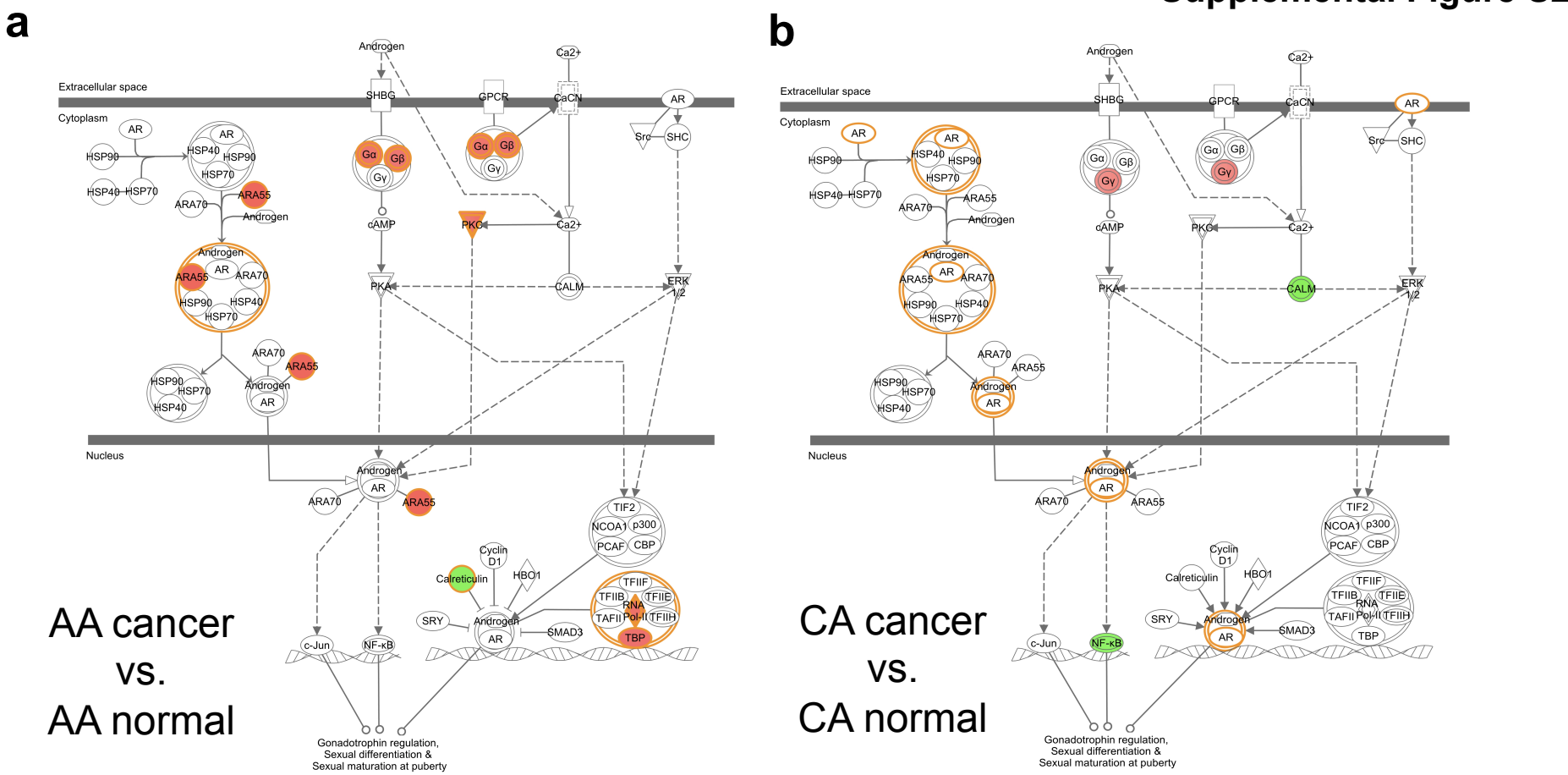
| Ingenuity Canonical Pathways | p-value |
|---|---|
| Antigen Presentation Pathway | 0.00025704 |
| Glutaryl-CoA Degradation | 0.000446684 |
| Serotonin Receptor Signaling | 0.00162181 |
| Virus Entry via Endocytic Pathways | 0.003019952 |
| G-Protein Coupled Receptor Signaling | 0.005011872 |
| cAMP-mediated signaling | 0.00616595 |
| Protein Ubiquitination Pathway | 0.007413102 |
| IL-15 Production | 0.008912509 |
| tRNA Splicing | 0.010964782 |
| Fatty Acid β-oxidation I | 0.010964782 |
| Purine Nucleotides De Novo Biosynthesis II | 0.012882496 |
| Cardiac β-adrenergic Signaling | 0.015488166 |
| Glutamate Removal from Folates | 0.016218101 |
| Asparagine Biosynthesis I | 0.016218101 |
| Interferon Signaling | 0.016982437 |
| IL-12 Signaling and Production in Macrophages | 0.019054607 |
| Mechanisms of Viral Exit from Host Cells | 0.025703958 |
| JAK/Stat Signaling | 0.02917427 |
| mTOR Signaling | 0.030549211 |
| Sulfate Activation for Sulfonation | 0.031622777 |
| ERK/MAPK Signaling | 0.033036954 |
| Endoplasmic Reticulum Stress Pathway | 0.033113112 |
| Integrin Signaling | 0.035237087 |
| FGF Signaling | 0.040271703 |
| Polyamine Regulation in Colon Cancer | 0.043651583 |
| Phototransduction Pathway | 0.045708819 |
| Spermidine Biosynthesis I | 0.047863009 |
| Crosstalk between Dendritic Cells and Natural Killer Cells | 0.047863009 |
| tRNA Charging | 0.047863009 |

# Supplemental Figure S1



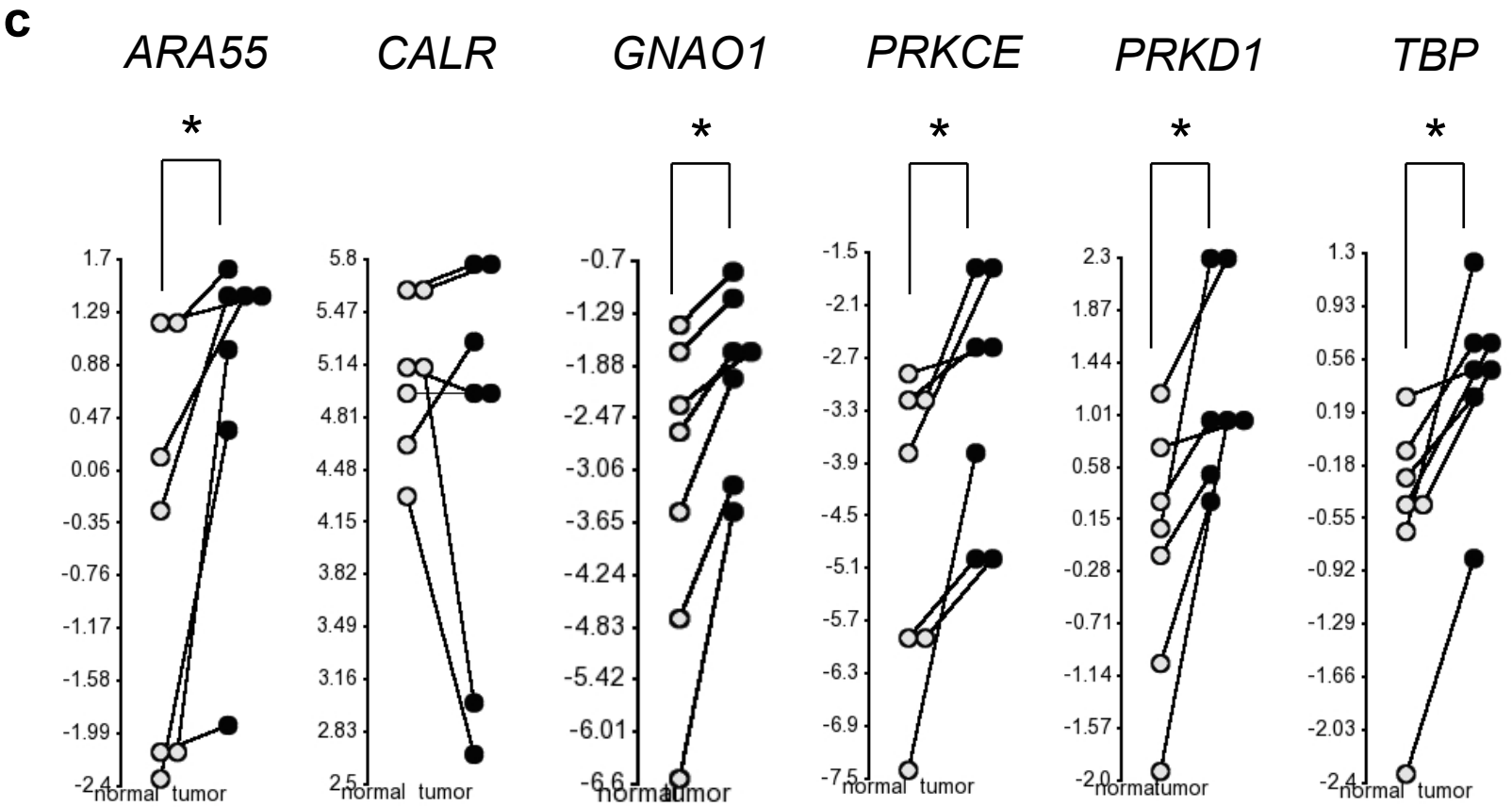

**Supplemental Figure S1.** Principal component analysis (PCA) of prostate tissue samples based on mRNA expression. Three-dimensional PCA plots demonstrate the separation of mRNA expression patterns, based on the differentially expressed genes, between (**a**) AA tumor specimens and AA matched normal counterparts (with 52.7% of the variance), and (**b**) CA tumor specimens and CA matched normal counterparts (with 63.2% of the variance). Tumor samples and matched normal tissue samples from AAs or CAs were indicated in red (•) and blue (•), respectively.

**Supplemental Figure S2**



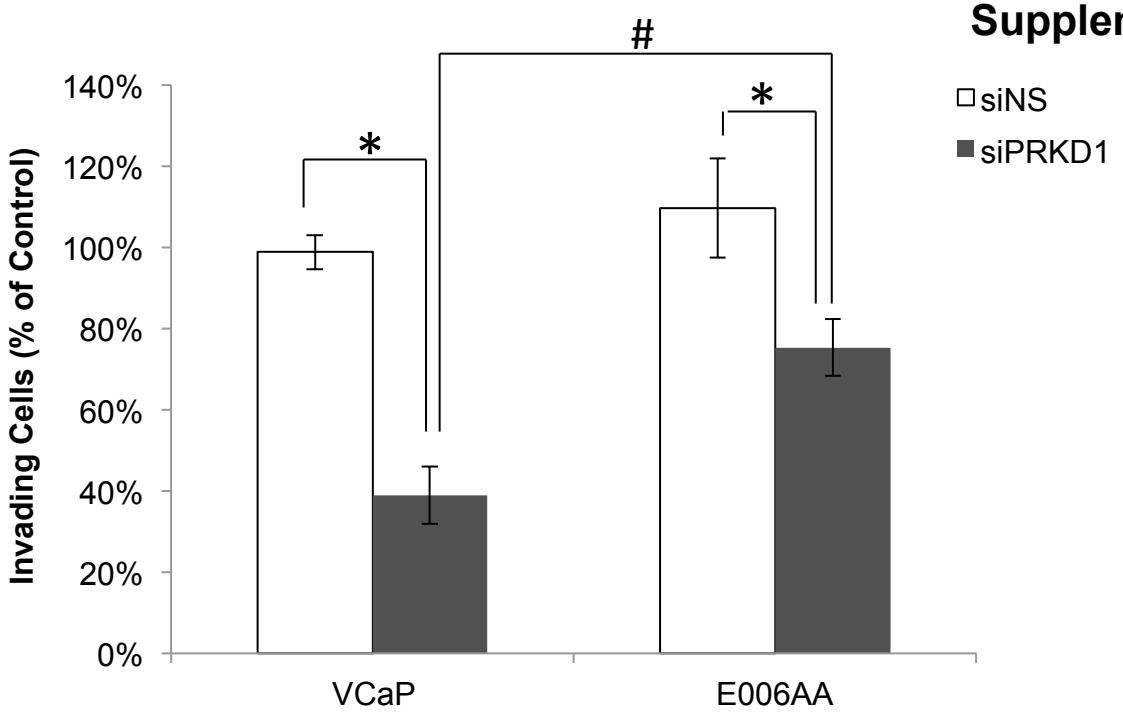

**Supplemental Figure S2a and 2b. Over-representation of differentially expressed genes in the AR signaling pathway of AA PCa specimens. (a)** Up-regulation of the AR signaling pathway in PCa from AA men. *ARA55*, *GNAO1, GNB3, PRKCE, PRKD1* (*PKCmu*), *POLR2L,* and *TBP* (genes encoding ARA55, G-protein alpha activating polypeptide O, G-protein beta polypeptide 3, PKC and RNA polymerase II polypeptide L, protein kinase C epsilon, protein kinase D1 (also called PKCμ) and TATA box binding protein, respectively) were up-regulated (shown in red), whereas *CALR* (gene encoding calreticulin) was down-regulated (shown in green) in 20 AA PCa specimens compared to 20 AA patient-matched normal prostate tissues. There was a statistically significant ($P < 0.05$) over-representation of differentially expressed genes in the AR signaling pathway. **(b)** In contrast, *GNG2, GNG11* and *GNG12* genes (encoding G protein gamma 2, 11 and 12) were up-regulated, and *CALM1* and *NFKB2* (genes encoding calmodulin 1 and NF-κB2) were down-regulated in 15 CA PCa specimens compared to 15 CA patient-matched normal prostate tissues. In this case there was not a significant ($P > 0.05$) over-representation of differentially expressed genes in the AR pathway.

**Supplemental Figure S2**



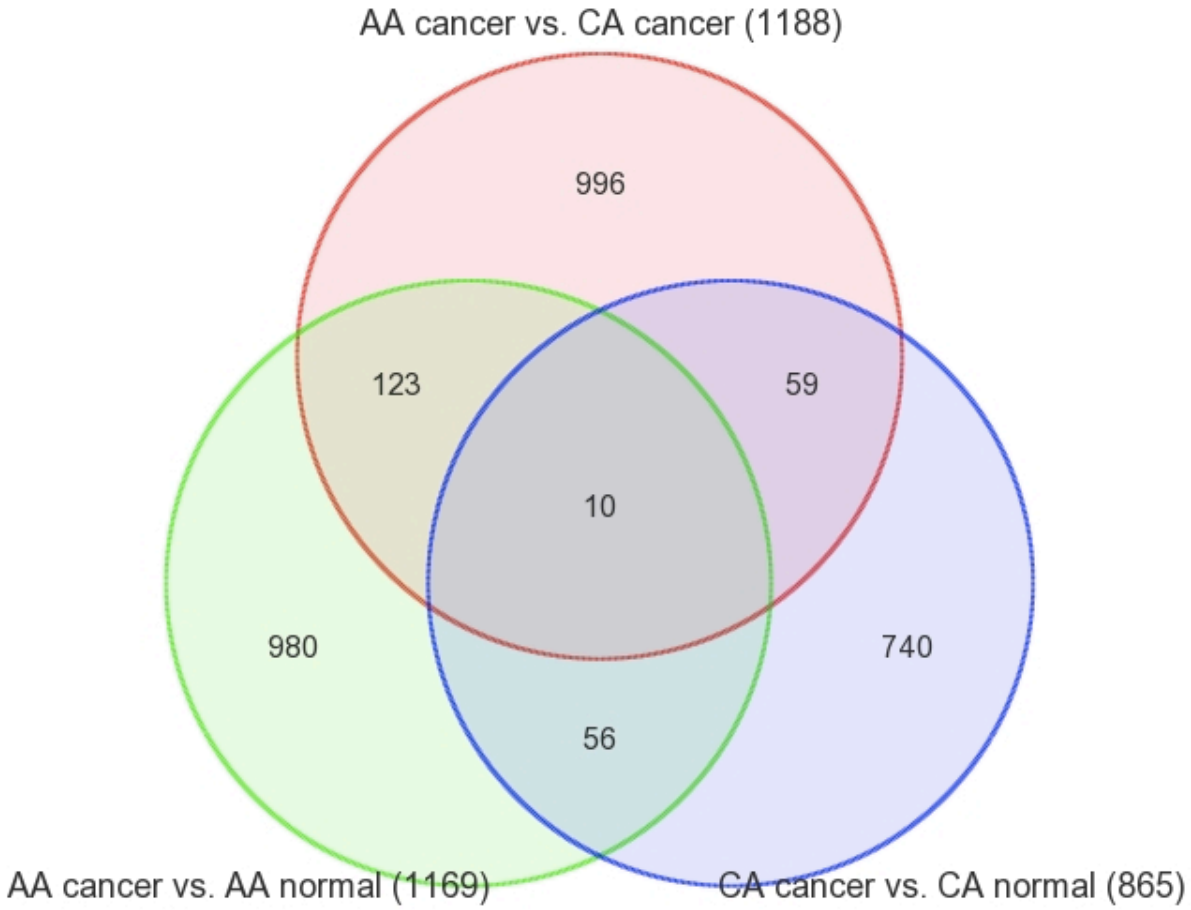

**Supplemental Figure S2c. Over-representation of differentially expressed genes in the AR signaling pathway of AA PCa specimens. (c)** qRT-PCR validation of *ARA55*, *GNAO1, GNB3, PRKCE, PRKD1, POLR2L,* and *TBP* expression levels in AA cancer specimens (close circle) and their matched normal tissues (open circle). *Significant different ($P < 0.05$, t-test) between AA cancer and AA matched normal. Each point represents relative expression level, determined by the $2^{-\Delta Ct}$ value, from each individual patient specimen.

## Supplemental Figure S2



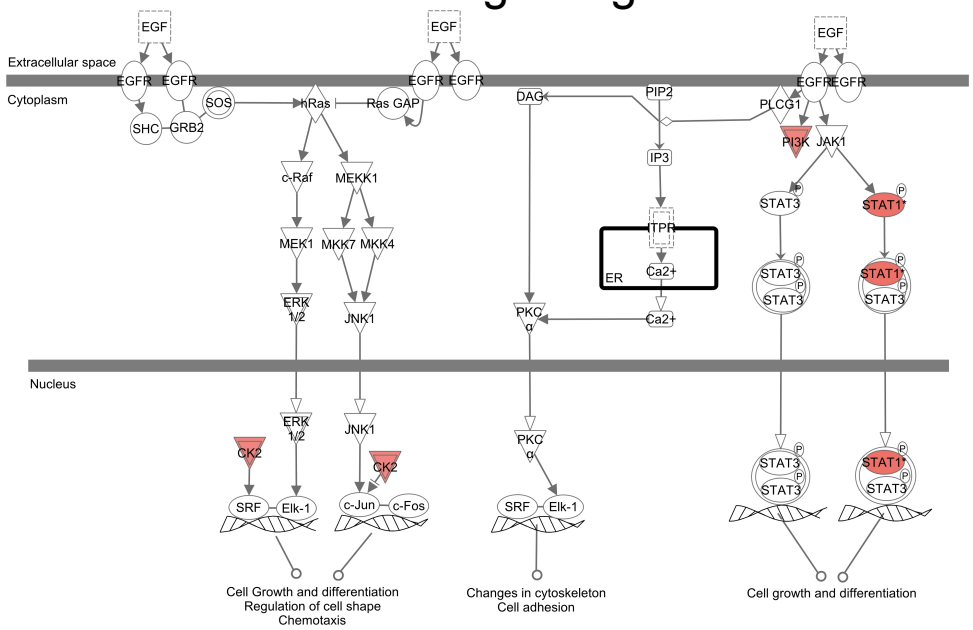

**Supplemental Figure S2d. The invasive potential of African American PCa cell line E006AA is resistant to *PRKD1* knockdown.** *ARA55, GNAO1, GNB3, POLR2L, PRKCE, PRKD1, TBP* and *CALR* were identified as differentially expressed genes in AA PCa versus patient-matched normal tissue (**Supplemental Figure S2**). These differentially regulated genes are found in the AR signaling pathway, and this pathway in AA PCa specimens was identified to be statistically over-represented with differentially expressed genes (note that the AR pathway in CA PCa was not found to be over-represented with differentially expressed genes). It should be noted that these 8 genes were not differentially expressed in a comparison of AA PCa versus CA PCa. Nor were these genes differentially expressed in CA PCa versus patient-matched normal tissue (**Supplemental Table S3**). Consequently, we decided to test the functional role of one of these genes in the AA PCa cell line E006AA and the CA PCa cell line VCaP. Targeted knockdown of *PRKD1* via siRNA resulted in a greater loss of invasive potential in VCaP compared to E006AA, as measured by matrigel assay. The ability of E006AA to be more resistant to an abrogation of invasive potential following *PRKD1* knockdown is hypothesized to be a compensatory mechanism mediated by the up-regulation of other genes (*ARA55, GNAO1, GNB3, POLR2L, PRKCE, TBP)* within the AR signaling pathway of AA PCa. Hence, a phenomenon known as synthetic lethality (i.e. knockdown of a combination of the up-regulated genes) may be required to fully abrogate invasive potential in the AA PCa cell line E006AA. These findings may explain the aggressive nature of PCa in the AA population. *Significantly different invasive capacity ($P < 0.05$, ANOVA, Tukey's post-hoc) between si*NS* and si*PRKD1* transfected cells. #Significantly different invasive capacity ($P < 0.05$, ANOVA, Tukey's post-hoc) between si*PRKD1* transfected VCaP and si*PRKD1* transfected E006AA cells.

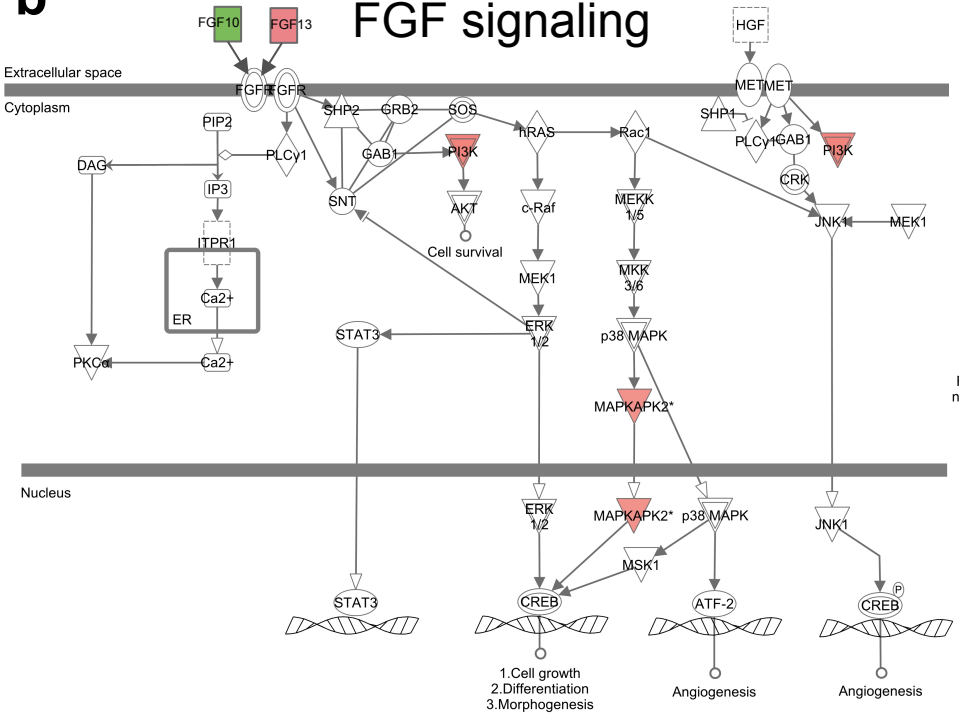
**Supplemental Figure S3**

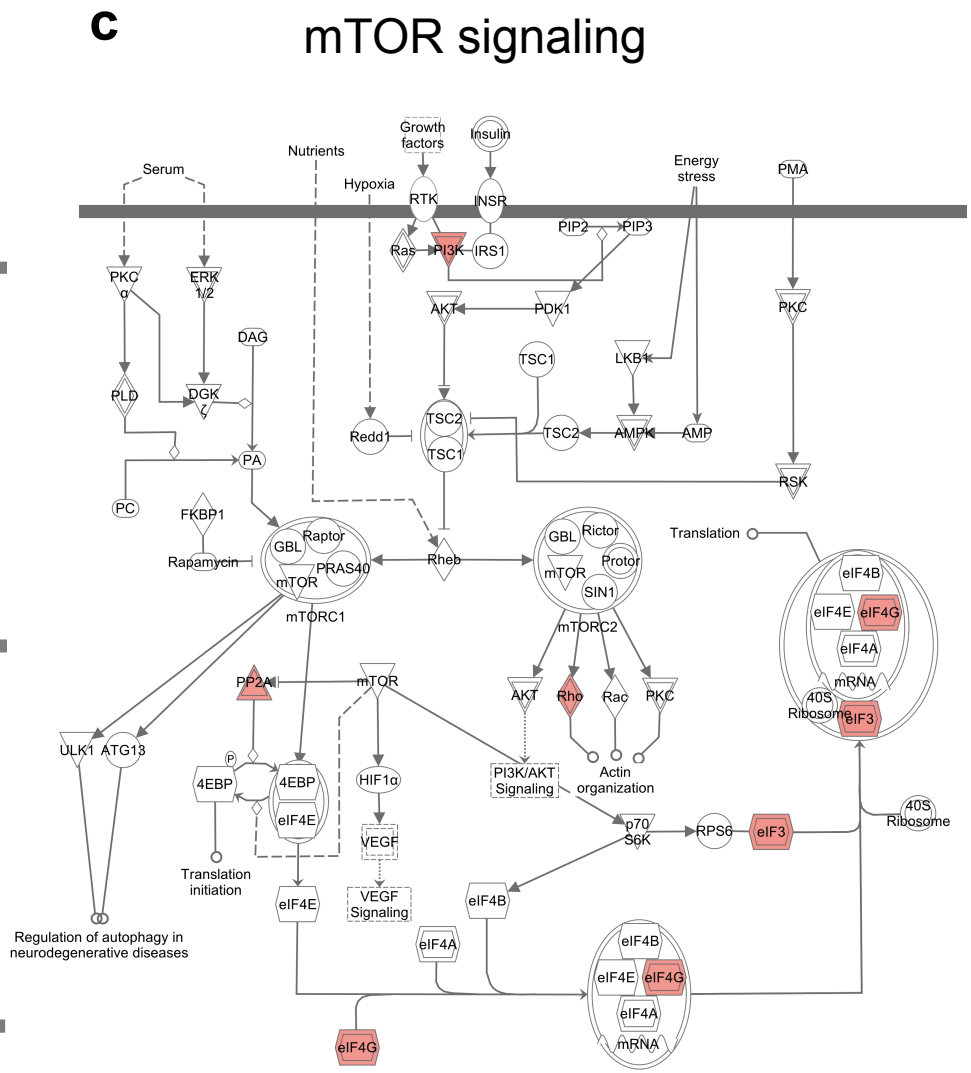



**Supplemental Figure S3.** Venn diagram depicting differentially expressed genes derived from paired comparisons of AA cancer versus AA matched normal (1169 genes), CA cancer versus CA matched normal (865 genes), and AA cancer versus CA cancer (1188 genes).

**Supplemental Figure S4**

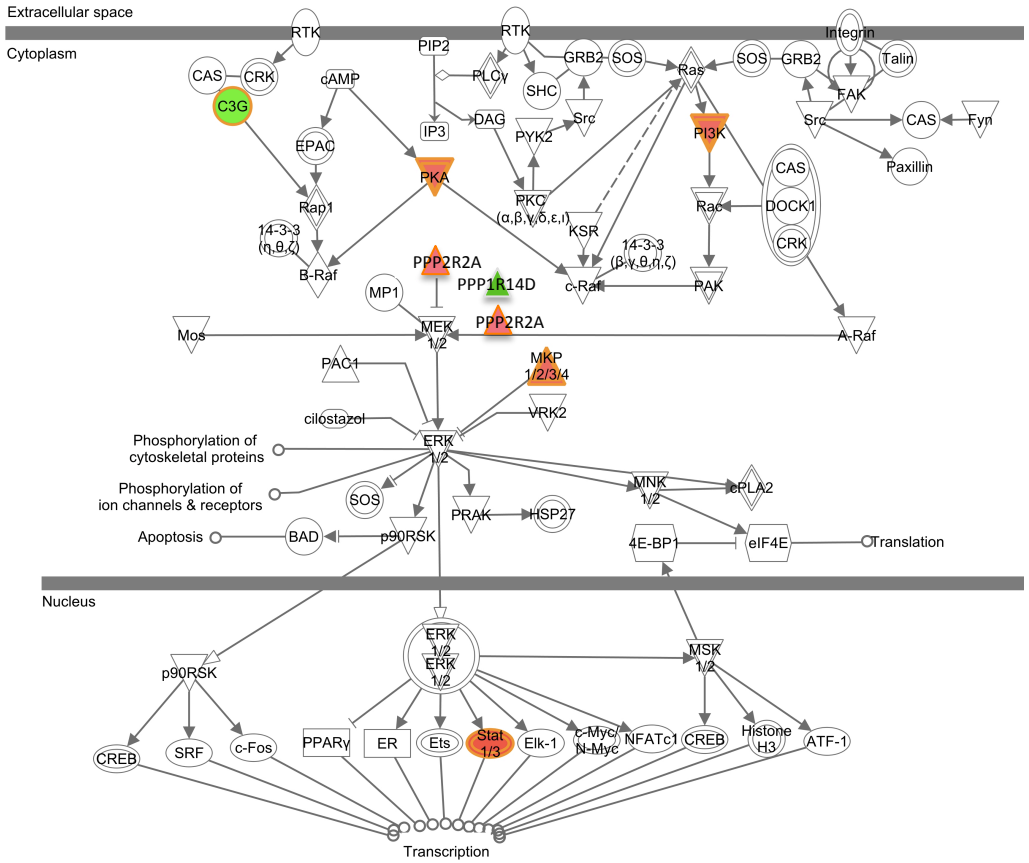


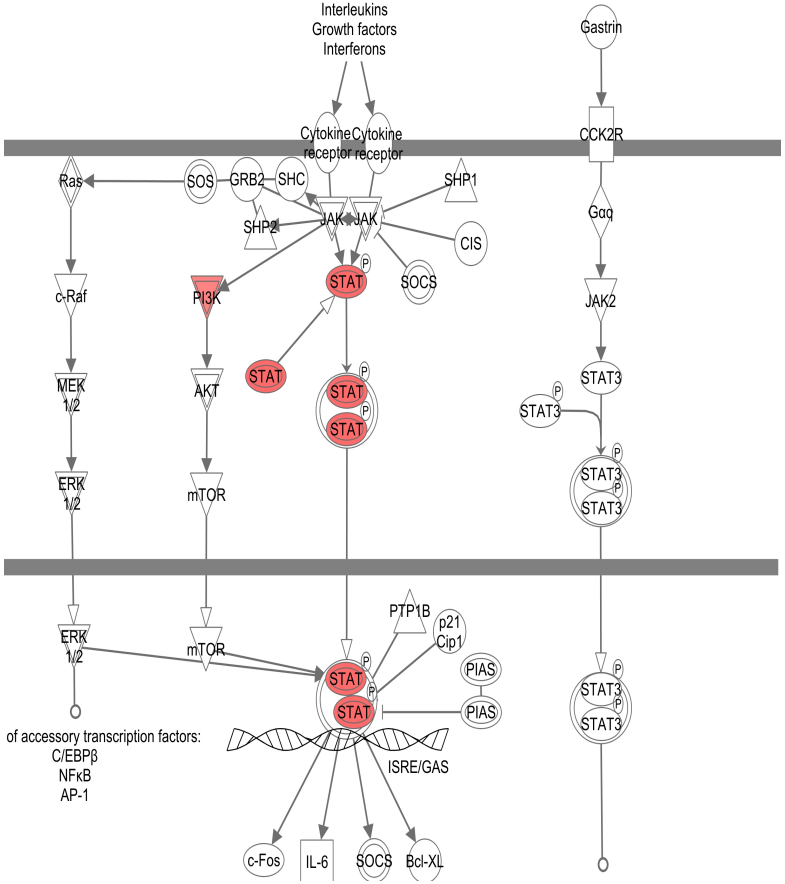



# Supplemental Figure S4

**d** ERK/MAPK Signaling

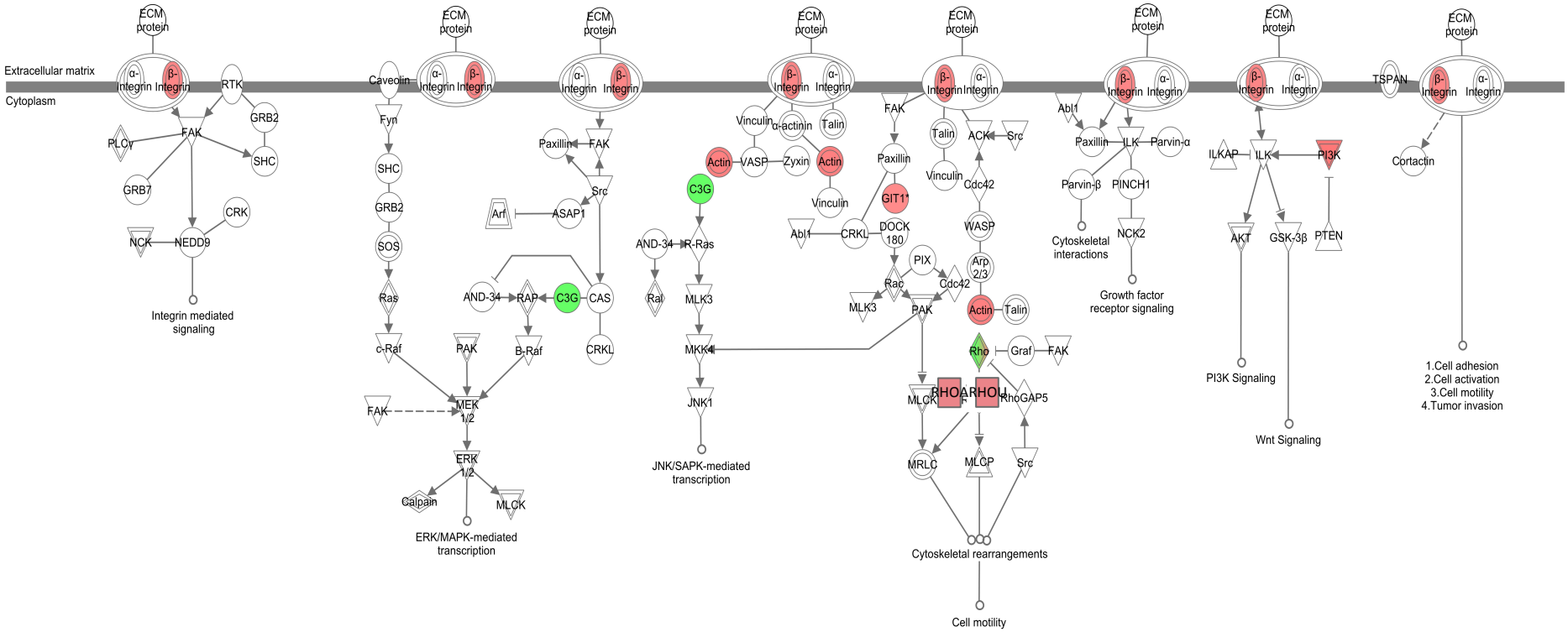



**e** JAK/STAT Signaling

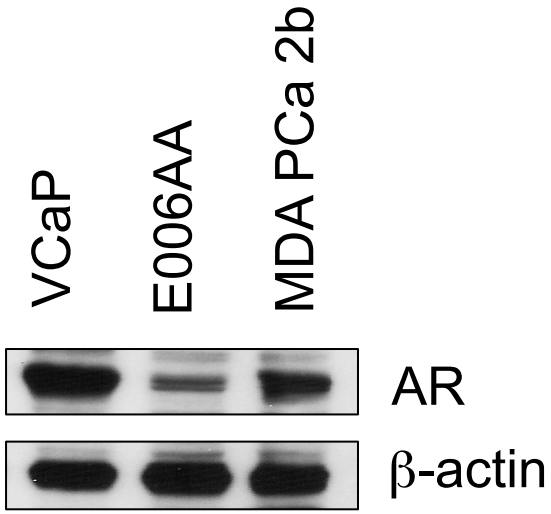


# Supplemental Figure S4

**f** Integrin Signaling

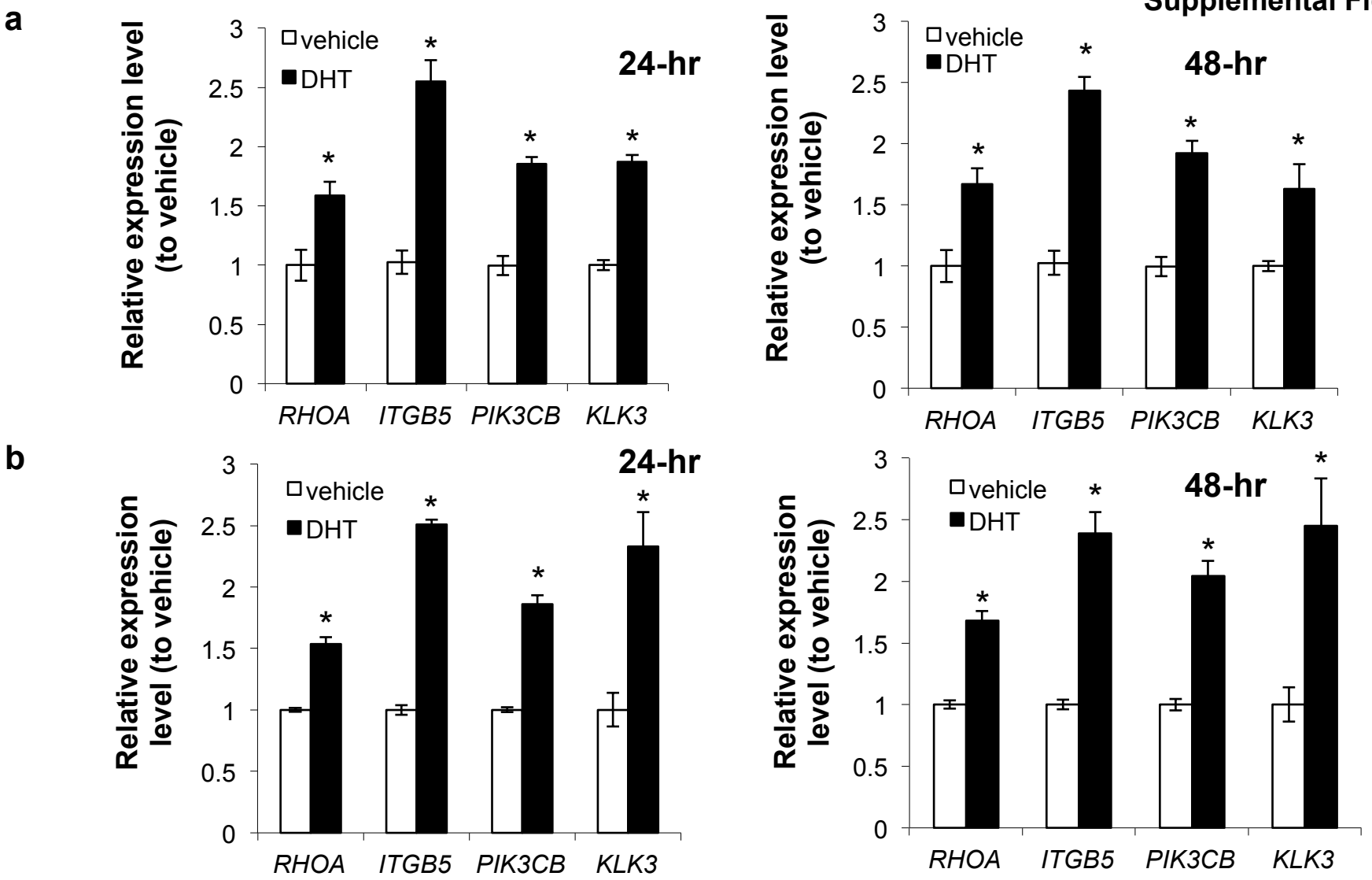



**Supplemental Figure S4. Canonical signaling pathways with a significant over-representation of differentially expressed AR-target genes.** EGF (a), FGF (b), mTOR (c), ERK/MAPK (d), JAK/STAT (e) and integrin (f) signaling pathways represent six of the significant ($P < 0.05$) canonical pathways over-represented with differentially expressed AR-target genes in PCa (a full list of over-represented pathways can be found in **Supplemental Table S6**). The overall up-regulation of AR-target genes (in AA PCa versus CA PCa comparisons) in these cancer-related signaling pathways suggests preferential oncogenic activity in AA PCa. Up-regulated (red) and down-regulated (green) genes in AA PCa versus CA PCa are indicated for the six canonical pathways.



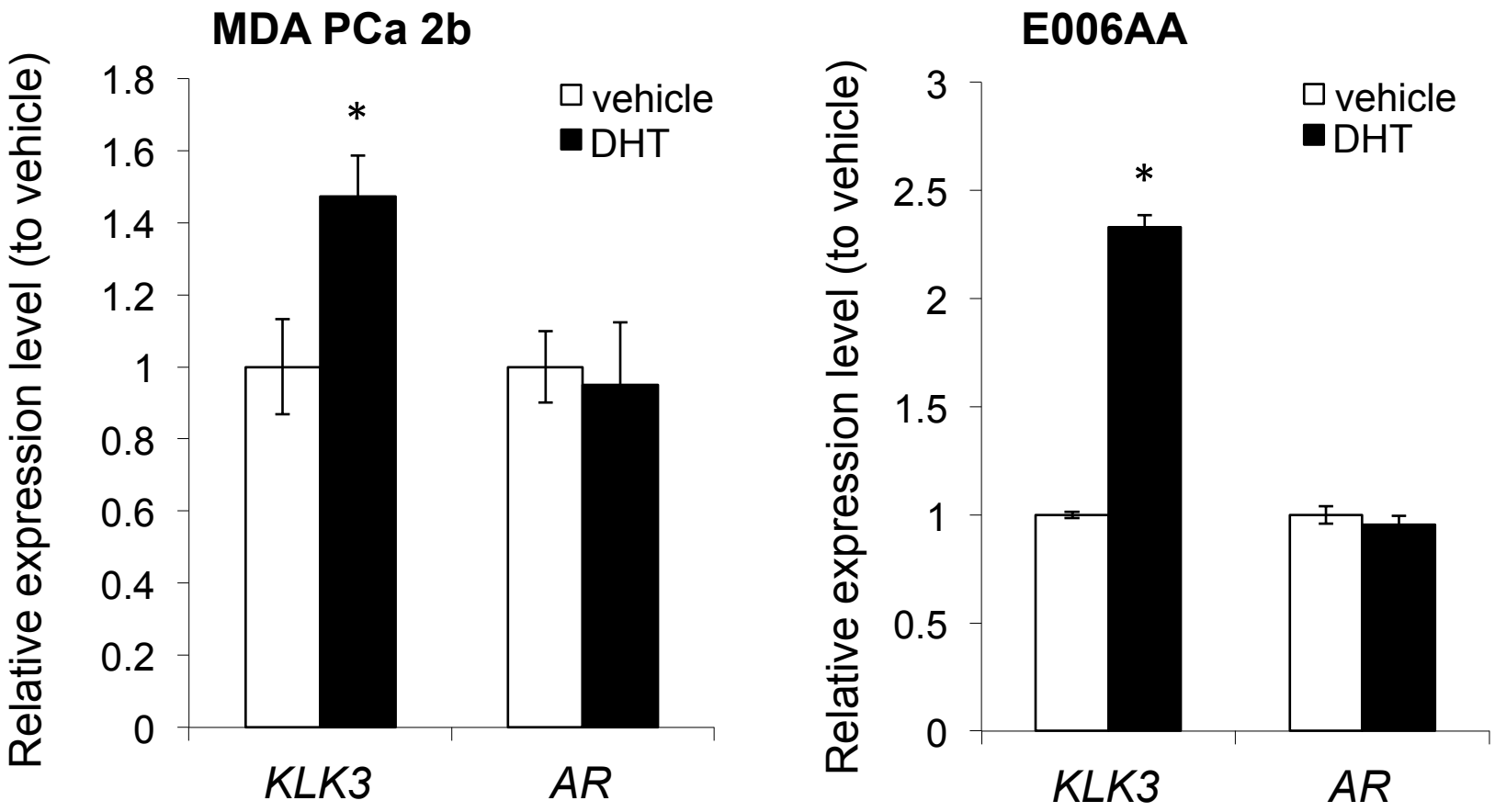

**Supplemental Figure S5. Western blot analysis of AR protein levels in a CA PCa cell line (VCaP) and AA PCa cell lines (E006AA and MDA PCa 2b)**. Three independent western blot assays were performed, and a representative blot depicting AR protein and β-actin is shown. β-actin was used as an endogenous protein control for the western blot analysis.

**Supplemental Figure S6**



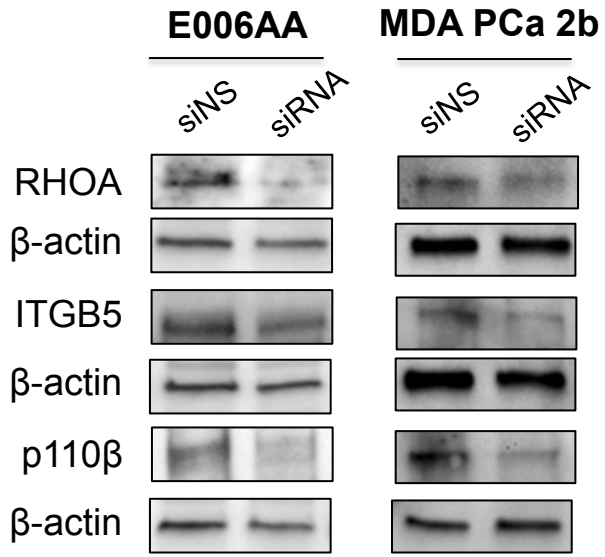

**Supplemental Figure S6. DHT-stimulated gene expression after 24-hr or 48-hr serum starvation.** qRT-PCR assays were performed to measure the relative expression levels of *RHOA, ITGB5, PIK3CB* and *KLK3* in MDA PCa 2b **(a)** and E006AA **(b)** in response to DHT treatment. The expression levels of *RHOA, ITGB5* and *PIK3CB* were determined using *EIF1AX* as endogenous genes for normalization. Cells were serum-starved for 24 hr (left panel) or 48 hr (right panel), then treated with a vehicle (<0.01% ethanol, open bar) or 100 nM DHT (close bar) for 18 hr prior to qRT-PCR assays. Data are represented as the mean ± SEM of 3-5 independent qRT-PCR experiments. *Significant increase of gene expression upon DHT treatment (P<0.05, t-test). However, no significant differences in DHT-stimulated gene expression were observed between cells undergoing 24-hr and 48-hr serum starvation (P> 0.05, t-test).

**Supplemental Figure S7**




**Supplemental Figure S7. Effect of DHT treatment on AR mRNA expression in AA PCa cell lines.** qRT-PCR assays were performed to measure the relative expression level of *AR* mRNA in MDA PCa 2b and E006AA. The relative expression levels of *AR* and *KLK3* were determined by using *EIF1AX* as endogenous genes for normalization. Cells were serum-starved for 24 hr, then treated with a vehicle (<0.01% ethanol final concentration) or DHT for 18 hr prior to qRT-PCR assays. Data are represented as the mean ± SEM of 3-5 independent qRT-PCR experiments. *Significantly increased gene expression of *KLK3* ($P < 0.05$, t-test), but not *AR* ($P > 0.05$, t-test), upon 100nM DHT treatment.

**Supplemental Figure S8**




**Supplemental Figure S8. Knockdown efficiencies of RHOA, ITGB5 and PIK3CB by siRNAs in PCa cells.** Western blot analysis of RHOA, ITGB5 and p110β (PIK3CB) protein levels in AA PCa cell lines (E006AA and MDA PCa 2b). Nonsense siRNA (siNS), or siRNA against *RHOA, ITGB5* or *PIK3CB* was transfected to E006AA and MDA PCa 2b cells. 24-hr after transfection, the cells were harvested and cell lysates were prepared for western blot analysis. β-actin was used as an endogenous protein control for the analysis. The image shown is representative of three independent experiments.