DKK1 defines a non-neuroendocrine subtype of mCRPC with low AR and low PSA expression

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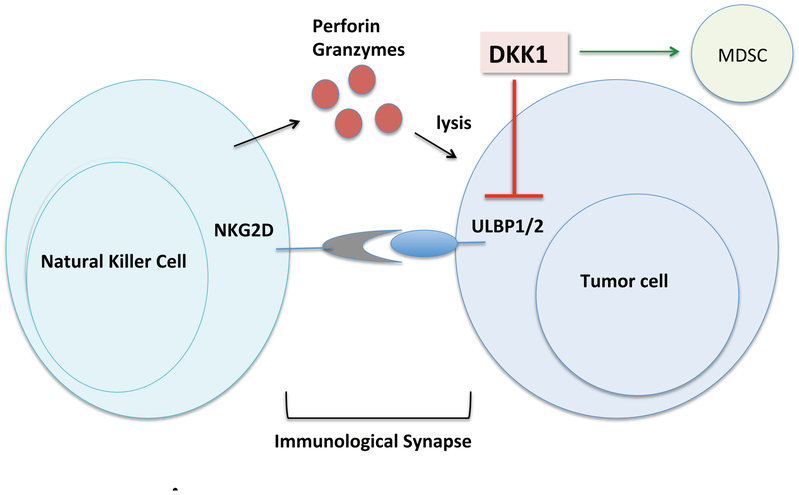
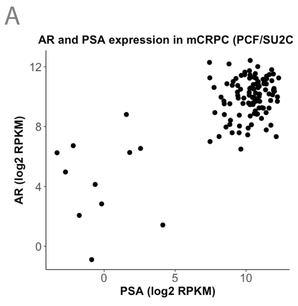
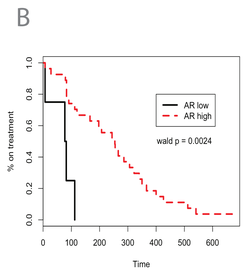
BACKGROUND

The biology underlying drug-resistant metastatic castration-resistant prostate cancer (mCRPC) has been linked to AR-dependent and independent mechanisms. The former is associated with histological adenocarcinoma whereas the latter has been the subject of significant controversy and has been associated with neuroendocrine histology. Here, we describe a subset of lethal prostate cancers that share the genomic features of AR-indifferent prostate cancer but are of adenocarcinoma histology and have low levels of AR and PSA expression. We further identify Dickkopf-1 (DKK1) as a therapeutically relevant biomarker to facilitate the diagnosis and expedite drug development for this disease.



DKK1 is a negative regulator of tumor immunity. DKK1 can be secreted by tumor cells and is downstream of multiple oncogenic signaling pathways including Wnt and Sox2. DKK1 can repress NK cell activation and has been associated with reduced levels of NK cell ligands. Secreted DKK1 can also promote myeloid-derived suppressor cell (MDSC) viability through represstion of MDSC canonical Wnt signaling.





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Gene	$AR^{low}PSA^{low}$ (% altered)	$AR^{high}PSA^{high}$ (% altered)	P value
RB1	50%	4%	< 0.0001
TP53	80%	51%	0.1
AR	0%	62%	< 0.001

	$AR^{low}PSA^{low}$	$AR^{high}PSA^{high}$	P value
Percent Histological Tumor Content	0.66	0.60	0.39

Federally Funded Research

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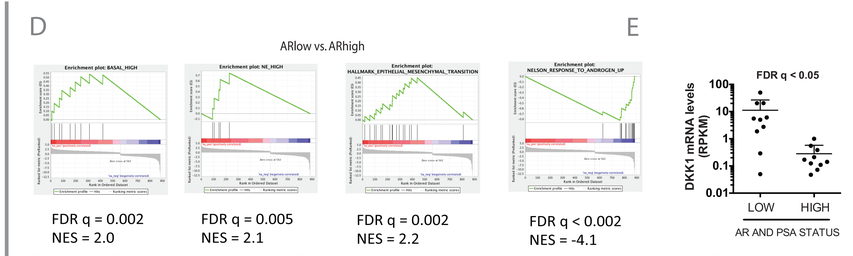
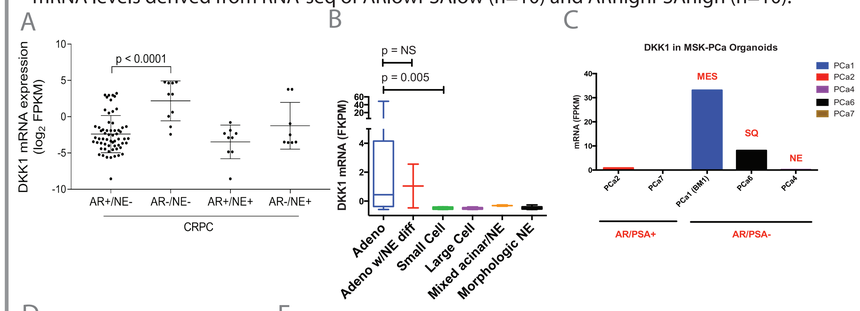


Figure 1. Discovery cohort for DKK1 upregulation in non-neuroendocrine mCRPC with low AR A. RNA sequencing of 150 mCRPC biopsies from SU2C/PCF cohort, AR and PSA mRNA levels are shown. B. Time on treatment Kaplan-Meier survival analysis of patients with ARlowPSAlow pre-treatment biopsies (n=4) compared with the remainder of the cohort (n=31). C. Genomic analysis of the specified genes in ARlowPSAlow (n=10) compared with the remainder of the cohort (n=140). D. GSEA analysis of ARlowPSAlow differentially expressed genes using custom-built gene sets. NE (Neuroendocrine), EMT (Epithelial-Mesenchymal Transition). E. DKK1 mRNA levels derived from RNA-seq of ARlowPSAlow (n=10) and ARhighPSAhigh (n=10).



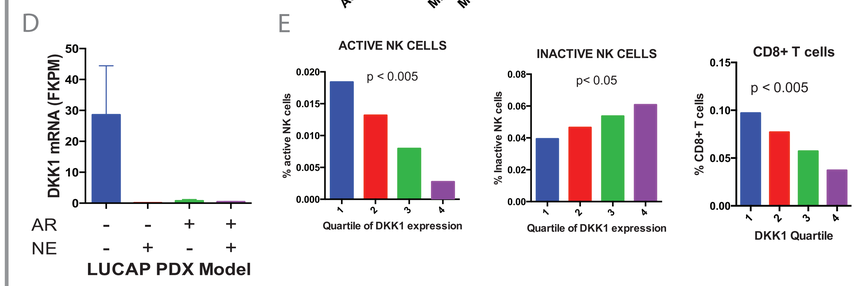


Figure 2. Validation cohorts for DKK1 upregulation in non-neuroendocrine mCRPC with low AR. A. DKK1 mRNA levels derived from RNA-seq of mCRPC subdivided by AR and Neuroendocrine gene signatures from Fred Hutchinson Cohort. B. DKK1 mRNA levels derived from publicly available RNA-seq from Weill-Cornell Medical College mCRPC cohort. C. DKK1 mRNA levels derived from RNA-seq of mCRPC-derived organoids. D. DKK1 mRNA levels derived from LUCAP PDX models. E. Cibersort2 analysis of SU2C/PCF cohort (n=150) subdivided by quartile of DKK1 mRNA expression using default immune cell gene expression signatures.

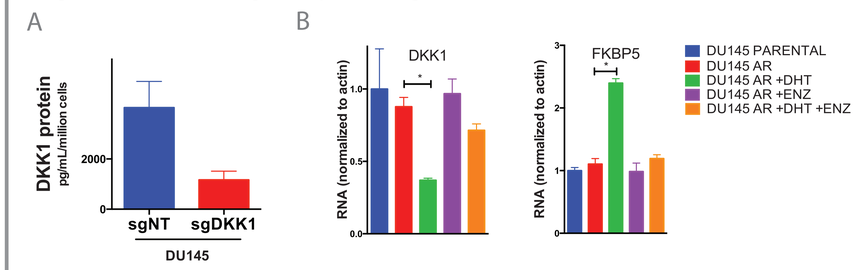


Figure 3. DKK1 is a secreted protein that can be repressed by active AR. A. DKK1 protein levels in DU145 cell culture medium analyzed with ELISA in cells expressing control (sgNT) and DKK1-targeted (sgDKK1) CRISPR guides. B. DKK1 and FKBP5 (AR target genes) RNA collected from DU145 cells expressing AR cDNA treated DHT, ENZ, or the combiation.

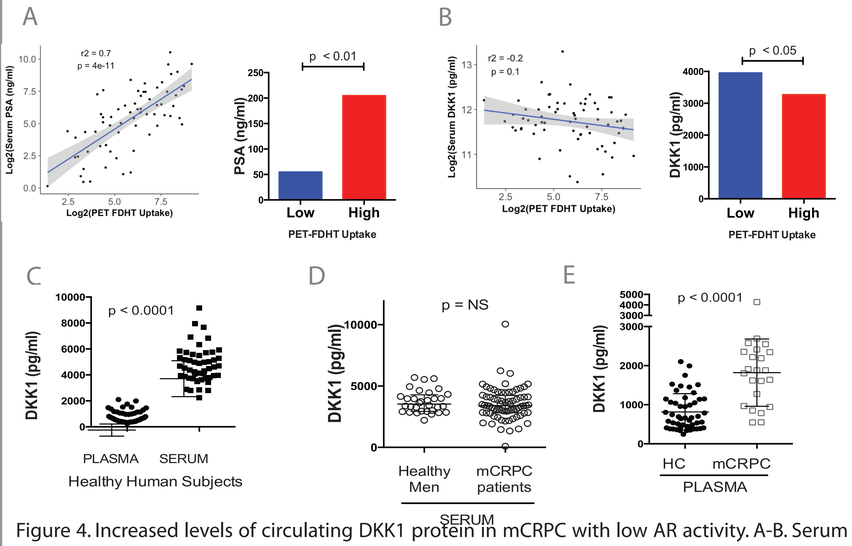


Figure 4. Increased levels of circulating DKK1 protein in mCRPC with low AR activity. A-B. Serum PSA (C) and DKK1 (D) analysis plotted against the sum FDHT SUV for mCRPC patients (n=70). C. DKK1 protein quantitated in healthy human subject serum and plasma. D. Serum DKK1 protein quantiated in Healthy men and mCRPC patients. E. Plasma DKK1 protein quantitated in healthy controls and mCRPC patients.

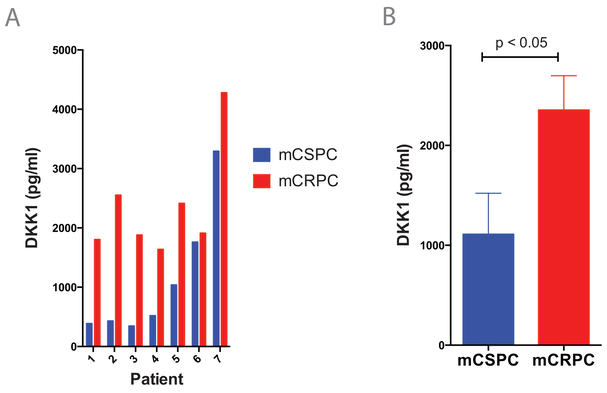


Figure 5. Plasma DKK1 is elevated in mCRPC A. Plasma DKK1 protein quantitated in treatment naïve mCSPC patients and matched samples from onset of mCRPC. B. Aggregate analysis of data

SUMMARY

- mCRPC with low AR and low PSA is a drug resistant entity and unmet medical need
- Lethal mCRPC with low AR and low PSA can be of non-neuroendocrine histology
- We show that lethal mCRPC with low AR and low PSA disproportionately expresses DKK1
- Circulating DKK1 is a marker of tumors with low AR activity
- Plasma represents the circulating fluid with best specificity for identifying patients with mCRPC
- Plasma DKK1 might enable early diagnosis of mCRPC with low PSA and could facilitate drug

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