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-independent 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.

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 ARRowPSAlow pre-treatment biopsies (n=4) compared to the remainder of the cohort (n=33). C. Genomic analysis of the specified genes in ARRowPSAlow (n=10) compared to the remainder of the cohort (n=140). D. ESRRA analysis of ARRowPSAlow differentially expressed genes using custom built gene sets. NE (Neuroendocrine), EMT (Epithelial-Mesenchymal Trans) E: DKK1 mRNA levels derived from RNA-seq of ARRowPSAlow (n=10) and ARRowPSAhigh (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 Hutchison Cohort B. DKK1 mRNA levels derived from publicly available RNA-seq from Weill-Cornell Medical College mCRPC cohort. C. DKK1 RNA levels derived from similar DKK1 mRNA levels derived from LEUCP/PDX model. D. DKK1 mRNA levels derived from LEUCP/PDX model. E. (Gibson et al) analysis of SU2C-PCF cohort (n=150) subdivided by quartile of DKK1 mRNA expression using default immune cell gene expression signatures.

Figure 3. Plasma DKK1 is elevated in mCRPC. A. Plasma DKK1 protein quantitated in treated naive mCRPC 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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