Increased Dickkopf-1 (DKK1) is a feature of metastatic non-neuroendocrine castration-resistant prostate cancer with low PSA

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Background: Advanced stage mCRPC can manifest AR-signaling independent growth typified by loss of AR and/or PSA expression in the absence of neuroendocrine (NE) features on biopsy. We sought to identify therapeutically relevant biomarkers of this highly resistant prostate cancer subtype.

Methods: An unbiased differential gene expression analysis of non-neuroendocrine mCRPC biopsies was carried out comparing patients with AR^{low} to patients with AR^{high} disease in a discovery cohort and validation cohort. The AR and NE status of the biopsies were defined by AR and PSA mRNA expression and gene signatures representative of AR activity and NE lineage. An RNA sequencing-based signature of immune cell subsets was calculated using the *Cibersort* algorithm.

Results: Differential gene expression analysis identified the secreted Wnt antagonist, DKK1, as significantly upregulated in AR^{low} cases compared to AR^{high} cases in our discovery cohort and confirmed in our validation cohort. Consistent with the role of DKK1 as a negative modulator of anti-tumor immunity, patient biopsies with the highest quartile of DKK1 expression showed an RNA signature consistent with lower levels of active NK cells, and lower levels of CD8+ T cells compared to those with the lowest quartile of DKK1 expression. DHT treatment of DU145 cells transduced with a retroviral construct overexpressing AR led to a reproducible reduction in DKK1 levels that could be reversed by the addition of the AR antagonists, enzalutamide. Duplex DKK1 and PSA RNA in–situ hybridization of metastases from a single patient with mCRPC shows that in liver and lung metastasis, DKK1 and PSA are expressed in a distinct and non-overlapping patter but isolated PSA expression was detected in bladder and lymph node metastases. In a separate cohort of patients, plasma DKK1 was significantly higher in mCRPC patients compared to healthy men and compared to men with mCSPC.

Conclusions: DKK1 represents a secreted biomarker that is disproportionately enriched in non-neuroendocrine mCRPCs that lack AR expression. Because DKK1 has been implicated as a suppressor of anti-tumor immunity, has been previously shown to have anti-tumor activity, and is a target of an existing neutralizing antibody, our results support the clinical evaluation of the role of DKK1 blockade in DKK1-positive AR-negative prostate cancer.

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