Title: KLF5 drives double-negative prostate cancer through a mixed basal, club, and hillock cell identity

Authors: Pitzen SP, Qiu Y, Zhang W, Munro SA, Dehm SM

While the majority of localized prostate cancer can be cured with surgery or radiation, metastatic disease is lethal. Therapies targeting the androgen receptor (AR) are initially effective for treating metastatic disease, but eventually men will develop castration resistant prostate cancer (CRPC). About 70-75% of CRPC displays restored AR signaling (“ARPC”), while the remaining 25-30% display lineage plasticity evidenced by the emergence of AR-negative subtypes like neuroendocrine CRPC (“NEPC”) displaying neuroendocrine (NE) markers, or “double negative” CRPC (“DNPC”) lacking both AR and NE markers. These AR independent manifestations of CRPC represent a clinical challenge because no effective therapies are available and therapeutic targets are largely unknown. Through analysis of publicly-available transcriptome data from clinical CRPC specimens, we found that DNPC tumors display gene expression features that define basal, club, and hillock cells of the benign prostate epithelium. Importantly, these cell types are inherently AR-negative and can survive castration in mice. Using a database of all known transcriptional regulators, we nominated the stem cell transcription factor KLF5 as a potential master regulator of basal, club, and hillock cell identities in CRPC. In cell line models of DNPC, knock down of KLF5 inhibited cell growth and reduced the expression of genes defining basal, club, and hillock cell identities. This work links a prevalent and poorly-defined subtype of AR-negative CRPC to AR-negative epithelial cell identities that normally exist in benign prostate. Inhibition of KLF5 and its downstream effectors could represent a therapeutic strategy to prevent or delay lineage plasticity and thereby extend patient response to AR-targeted therapies.