Epigenomic profiling of circulating chromatin for early detection and monitoring of neuroendocrine prostate cancer

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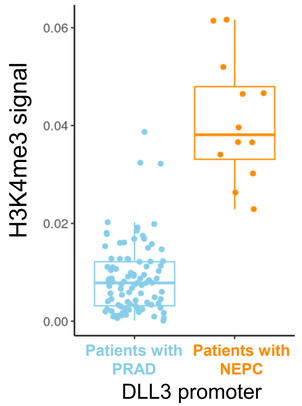
Background

- Neuroendocrine prostate cancer (NEPC) is an aggressive subtype of prostate cancer that can arise due to the selective pressure of androgen blockade. Early detection of NEPC has prognostic and therapeutic implications but remains challenging.
- Neuroendocrine (NE) transformation is spatially heterogeneous, with co-existing NE and adenocarcinoma (AD) components across a patient's disease burden, leading to underdiagnosis using tumor biopsy.
- Moreover, treatment response assessment with cross-sectional imaging cannot distinguish changes in co-existing NE and AD components.
- To address these challenges, we developed a non-invasive approach to monitor NE transformation in patients with prostate AD (PRAD) through profiling of circulating chromatin.

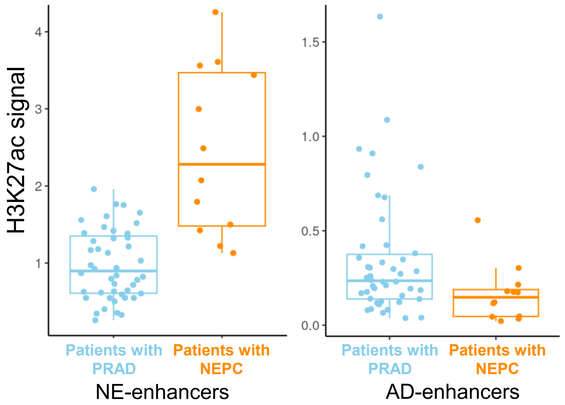
Methods

- A total of 40 plasma samples were collected longitudinally from 5 patients initially diagnosed with PRAD who later developed NEPC at the Dana-Farber Cancer Institute.
- Chromatin immunoprecipitation and sequencing on cell-free DNA (cfChIP-seq) was performed for H3K4me3 and H3K27ac at Precede Biosciences.
- To separately quantify circulating chromatin derived from NE and AD components in a given patient, we measured H3K27ac at NE-specific (NE-score) and AD-specific regulatory elements (AD-score), respectively, derived from differential peaks analysis on LuCaP PDXs H3K27ac ChIP-seq data.
- The proportion of NE and AD was calculated for each plasma sample drawn throughout the course of patients' disease.
- Whole genome sequencing was performed to estimate the cfDNA tumor fraction using ichorCNA.
- In silico dilution of independent LuCaP PDXs and plasma samples was then performed to validate our results.

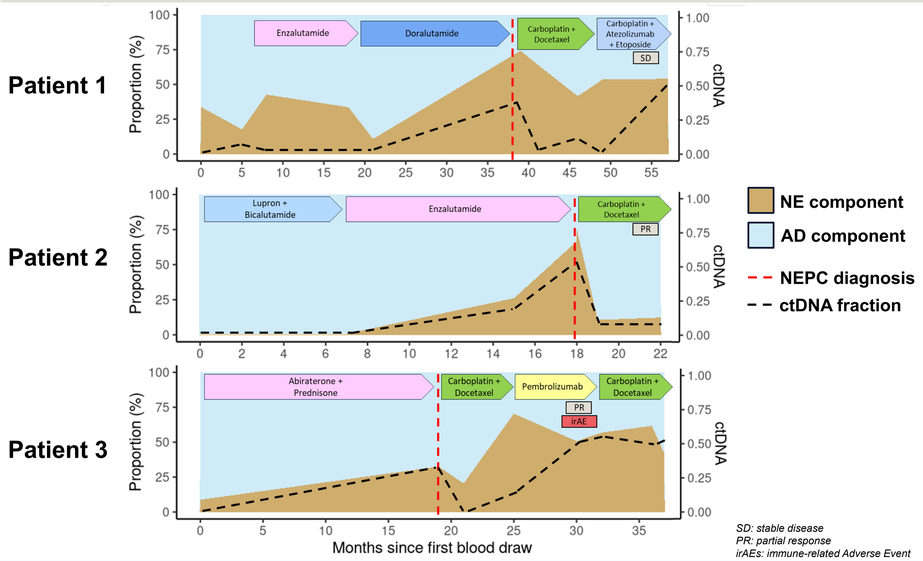
cfChIP may infer expression of targetable genes in NEPC



Comparison of H3K27ac signal at NE- and AD-enhancers between plasma samples from PRAD and NEPC patients

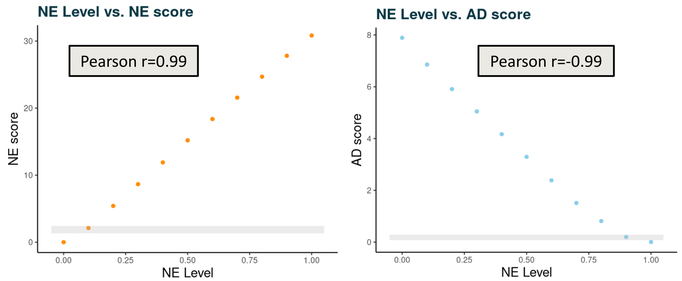


Examples of variation in NE- and AD-derived circulating chromatin over the course of treatment



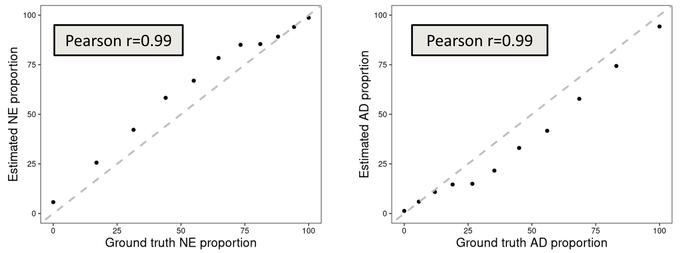
In silico dilution of NEPC and PRAD PDXs

In silico dilution was performed on one NEPC LuCaP and one PRAD LuCaP PDX that are separate from samples used to define NE/AD enhancers, with tracking of NE and AD scores for each dilution level.



In silico dilution of NEPC and PRAD plasma

In silico dilution of one NEPC plasma sample (with 0.88 ctDNA) and one PRAD plasma sample (with 0.49 ctDNA). cfChIP reads were mixed at the portions indicated on x-axis, and NE/AD portions were calculated as indicated on the y-axis.



Conclusion

Epigenomic profiling of circulating chromatin may enable early detection of NEPC and monitoring of NE and AD components in metastatic prostate cancer.

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