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PROSTATE CANCER

Multilayered mutation analysis indicates divergent clonal evolution

> Unsupervised analysis … showed clear epigenetic segregation between the CRPC subtypes

New genomic and epigenomic data of samples from patients with metastatic castration-resistant prostate cancer (CRPC) suggest that differentiation into neuroendocrine subtypes from adenocarcinoma precursors follows a divergent evolution pattern, characterized by epigenetic modulation. Based on their results, the researchers developed a molecular 70-gene classifier to enable improved diagnosis of neuroendocrine CRPC.

The development of resistance to androgen-receptor (AR)-targeted therapies in advanced prostate cancers has been proposed to involve pathways of epithelial plasticity, resulting in tumour cells with neuroendocrine morphological features and considerably reduced AR expression. However, the molecular mechanisms underlying this differentiation remain incompletely understood. In a new report published in *Nature Medicine*, Himisha Beltran, Davide Prandi, and colleagues studied 114 biopsy samples from 81 men with metastatic CRPC, including 51 specimens with adenocarcinoma features and 30 specimens with neuroendocrine features. For 17 patients, multiple samples were available. Overall, samples with neuroendocrine features showed lower *AR* mRNA and AR protein expression than adenocarcinoma samples.

First, the researchers performed whole-exome sequencing and found that the spectrum of genomic mutations was, overall, similar between the two tumour subtypes but with some distinct differences, for example, more common loss of *RB1* and mutation or loss of *TP53,* as well as a lack of activating alterations affecting the *AR* gene or AR signalling, in neuroendocrine compared with adenocarcinoma samples.

To elucidate the evolutionary basis of differentiation to a neuroendocrine CRPC subtype, the team then investigated specimens that had been taken throughout patients' disease progression. The presence of distinct mutations among samples from specific patients suggested a high level of clonality regardless of subtype and, taken together with the overall similarity of genomic alterations, pointed towards divergent clonal evolution underlying the development of neuroendocrine CRPC cells from adenocarcinoma precursors.

Clinically, neuroendocrine CRPC is considered more aggressive than adenocarcinoma, which the finding of widespread genomic similarity of the two subtypes could not account for. Thus, the team evaluated the epigenetic profiles of their specimens to discover whether the phenotypic differences could be caused by changes in DNA methylation patterns. Unsupervised analysis of methylation sites showed clear epigenetic segregation between the CRPC subtypes. Altered DNA methylation in neuroendocrine CRPC could be mapped to functional processes, such as cell–cell adhesion and epithelial–mesenchymal transition. In addition, mRNA expression of histone methyltransferase *EZH2* was twofold higher in neuroendocrine CRPC than in adenocarcinoma, collectively suggesting a central role of epigenetic modulation in the development of the neuroendocrine CRPC subtype.

Finally, to overcome the current shortcomings in diagnosis of neuroendocrine CRPC, the team developed a scoring system based on the genomic, transcriptomic and epigenomic status of 70 genes, which had high precision and recall in identifying neuroendocrine CRPC across previously published datasets.

"This work has implications for clinical biomarker development," summarizes Beltran. "Earlier detection of neuroendocrine CRPC (potentially noninvasively, using circulating tumour cells or DNA) could improve patient selection for therapy."

Clemens Thoma

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