Detection and characterization of mismatch repair defective metastatic prostate cancer using circulating tumour DNA

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Background: DNA mismatch repair defects (MMRd) and tumor hypermutation are rare in metastatic prostate cancer. As such, the salient genomic and clinical features of this distinct disease subtype remain poorly characterized. Furthermore, since MMRd prostate cancers can respond to immune checkpoint inhibitors, there is an urgent need for practical MMRd detection tools.

Methods: We performed deep targeted sequencing of 1047 plasma cell-free DNA samples from patients with progressing metastatic prostate cancer. All hypermutated samples (>11 mutations per Mbp) and available archival tissue were also subjected to whole exome sequencing. In archival tissue, mismatch repair protein expression was assessed via immunohistochemistry (IHC).

Results: 665 samples from 434 patients had circulating tumor DNA (ctDNA) purity above 2% and were evaluable. 16 patients (3.7%) had MMRd etiology, evidenced by pathogenic alterations in *MSH2*, *MSH6*, or *MLH1* and/or a combination of somatic hypermutation, microsatellite instability, and characteristic trinucleotide signatures. Tissue mismatch repair protein IHC confirmed ctDNA-based predictions in all available samples. Tumor suppressors such as *PTEN*, *RB1*, and *TP53* were typically inactivated by mutation rather than copy number loss. Unlike mismatch repair intact prostate cancer, hotspot mutations in oncogenes such as *AKT1*, *PIK3CA* and *CTNNB1* were common, and the AR ligand binding domain was mutated in 9/16 patients. We observed high intra-patient clonal diversity, evidenced by subclonal driver mutations and dynamic shifts in mutation allele frequency over time. MMRd patients had a worse clinical prognosis than mismatch repair intact prostate cancer.

Conclusions: MMRd metastatic prostate cancer is associated with oncogene activation and subclonal diversity, which may contribute to a clinically aggressive disposition. In patients with detectable ctDNA, panel-based cell-free DNA sequencing is a practical tool to prioritize this subtype for immunotherapy.

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