Intratumoural evolutionary landscape of high-risk prostate cancer: The PROGENY study of genomic and immune parameters - DTU Orbit (29/12/2018)

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Background: Intratumoural heterogeneity (ITH) is well recognised in prostate cancer (PC), but its role in high-risk disease is uncertain. A prospective, single-arm, translational study using targeted multiregion prostate biopsies was carried out to study genomic and T-cell ITH in clinically high-risk PC aiming to identify drivers and potential therapeutic strategies.

Patients and methods: Forty-nine men with elevated prostate-specific antigen and multiparametric-magnetic resonance imaging detected PC underwent image-guided multiregion transperineal biopsy. Seventy-nine tumour regions from 25 patients with PC underwent sequencing, analysis of mutations, copy number and neoepitopes combined with tumour infiltrating T-cell subset quantification. Results: We demonstrated extensive somatic nucleotide variation and somatic copy number alteration heterogeneity in high-risk PC. Overall, the mutational burden was low (0.93/Megabase), but two patients had hypermutation, with loss of mismatch repair (MMR) proteins, MSH2 and MSH6. Somatic copy number alteration burden was higher in patients with metastatic hormone-naive PC (mHNPC) than in those with high-risk localised PC (hrlPC), independent of Gleason grade. Mutations were rarely ubiquitous and mutational frequencies were similar for mHNPC and hrlPC patients. Enrichment of focal 3q26.2 and 3q21.3, regions containing putative metastasis drivers, was seen in mHNPC patients. We found evidence of parallel evolution with three separate clones containing activating mutations of β-catenin in a single patient. We demonstrated extensive intratumoural and intertumoural T-cell heterogeneity and high inflammatory infiltrate in the MMR-deficient (MMRD) patients and the patient with parallel evolution of β-catenin. Analysis of all patients with activating Wnt/β-catenin mutations demonstrated a low CD8+/FOXP3+ ratio, a potential surrogate marker of immune evasion. Conclusions: The PROGENY (PROstate cancer GENomic heterogeneitY) study provides a diagnostic platform suitable for studying tumour ITH. Genetic aberrations in clinically high-risk PC are associated with altered patterns of immune infiltrate in tumours. Activating mutations of Wnt/β-catenin signalling pathway or MMRD could be considered as potential biomarkers for immunomodulation therapies.

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