Transcriptomic Stratification of Advanced Primary Endometrial Tumours According to Mismatch Repair Status

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BACKGROUND AND AIMS

Endometrial cancer (EC) is one of the most common gynaecological malignancies in high-income countries and is associated with poor outcomes in advanced stages.[1-3] The introduction of immune checkpoint inhibitors has substantially improved survival in patients with advanced tumours with mismatch repair deficiency (MMRd) and high microsatellite instability (MSI-H).[4,5] However, most ECs are mismatch repair–proficient (MMRp) and microsatellite stable (MSS),[6,7] and these tumours derive limited benefit from immunotherapy.[4,8,9] This represents a major unmet clinical need and underscores the importance of identifying alternative therapeutic targets and prognostic biomarkers for patients with advanced MMRp-MSS disease.

MATERIALS AND METHODS

The authors analysed clinical and transcriptomic data from The Cancer Genome Atlas Uterine Corpus Endometrial Carcinoma (TCGA-UCEC) cohort using the TCGABiolinks package in RStudio (Posit, Boston, Massachusetts, USA). Patients with primary advanced-stage EC and complete clinical, molecular, and RNA sequencing data were included. Tumours were classified according to mismatch repair and molecular subtype status. Differential gene expression analysis between MMRp-MSS and MMRd-MSI-H tumours was performed using DESeq2 library. Associations between gene expression levels and disease-specific survival (DSS) within the MMRp-MSS subgroup were assessed using Cox proportional hazards models. In the primary analysis, the MMRp-MSS group included tumours from the *POLE*-mutant, *TP53*-altered, and no-specific-molecular-profile subtypes. A prespecified sub-analysis was conducted, excluding *POLE*-mutant tumours, to evaluate the robustness of findings.

RESULTS

Of 545 patients in the cohort, 139 had advanced-stage disease and met the inclusion criteria, including 27 with MMRd-MSI-H tumours and 112 with MMRp-MSS tumours. There were no significant differences in DSS between the two groups. Differential expression analysis identified 974 genes that were significantly different between MMRp-MSS and MMRd-MSI-H tumours. Of these, 268 genes were significantly associated with DSS within the MMRp-MSS subgroup. Higher expression of genes involved in immune system activation and inhibition of Wnt signalling pathways was associated with improved survival. In contrast, increased expression of genes linked to oncogenic signalling, immune evasion, developmental reprogramming, cellular plasticity, neuronal-like differentiation, and extracellular matrix remodelling was associated with poorer outcomes. The sub-analysis excluding *POLE*-mutant tumours yielded consistent results.

CONCLUSION

In conclusion, advanced MMRp-MSS ECs exhibit a transcriptional landscape distinct from that of MMRd-MSI-H tumours. Within the MMRp-MSS subgroup, specific gene expression programmes are associated with clinical outcomes, highlighting biologically relevant pathways linked to both favourable and adverse prognosis. These findings provide insight into the molecular heterogeneity of advanced EC and identify potential therapeutic targets for patients with MMRp-MSS disease, a group with limited response to current immunotherapy approaches. The authors' results support the development of molecularly stratified treatment strategies and may inform future efforts to improve outcomes in this high-risk population.

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