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Tumor microenvironment features in extrapulmonary neuroendocrine carcinomas for predicting response to immunotherapy and platinum-based therapy

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BACKGROUND

Extrapulmonary neuroendocrine carcinomas (EP-NECs) are rare, aggressive, and poorly understood tumors that lack reliable biomarkers. Moreover, standard Ki-67 immunohistochemistry (IHC) does not always predict therapeutic response. To address this gap, we analyzed the tumor microenvironment (TME) transcriptome of EP-NEC to uncover markers of response to immunotherapy and platinum-based chemotherapy.

METHODS

The BostonGene (BG) Tumor Portrait® test was used to analyze 15 EP-NEC samples. Their signature scores were computed using modified ssGSEA and median-scaled relative to the BG NEC reference cohort. Each sample was then classified using the KNeighborsClassifier algorithm as immune-enriched, fibrotic; immune-enriched, non-fibrotic; fibrotic; or immune desert.

RESULTS

Three TME subtypes were identified: immune-enriched, non-fibrotic (n = 3), fibrotic (n = 8), and immune desert (n = 4). The immune-enriched TME was associated with favorable response to immunotherapy, while the immune desert TME was linked to disease progression (Fisher's p = 0.03). The partial response group showed at least a twofold higher concentration of CD4 and CD8 T-cells than the stable and progressive disease groups. No association was found between TME subtype and response to first-line therapy carboplatin/etoposide ± atezolizumab, while RNA-seq-derived MKI67 expression

showed a stronger correlation in stratifying response to platinum-based chemotherapy than Ki-67 IHC.

CONCLUSIONS

Transcriptomic profiling of the TME for EP-NEC revealed an immune-active TME corresponding to a greater likelihood of response to immunotherapy. Expandable to other cancer types, our approach can enhance patient stratification, treatment response prediction, trial design, and biomarker discovery.

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