39°CBU

Transcriptomic Features Associated with Recurrence in Upper Tract Urothelial Carcinoma (UTUC)

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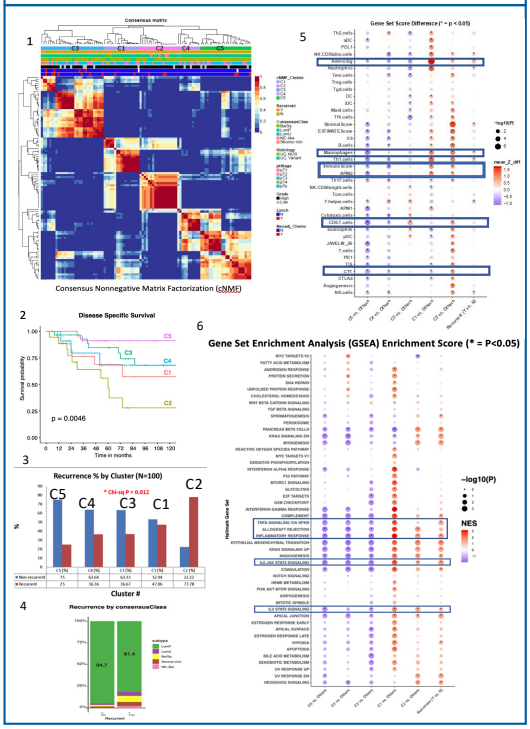
Introdução e Objetivo

- While upper tract urothelial carcinoma (UTUC) comprises only 5-10% of urothelial tumors[1], the 5-year disease specific survival rate is <50% for patients with pT2/T3 disease and <10% for patients with pT4 disease[2].
- Studying the molecular and genomic landscape of UTUC as a distinct entity from urothelial carcinoma of the bladder (UCB) has been important for the development of targeted therapies and can be helpful in improving risk-stratification, and guiding treatment selection.
- In this study, we aim to identify transcriptomic and genomic signatures that may help predict disease prognosis in patients with UTUC.

Método

- Total RNA was isolated using Trizol from frozen tissue blocks obtained from 100 patients with nonmetastatic UTUC that underwent radical nephroureterectomy (MSK100 cohort).
- TruSeq RNA Library Prep Kit v2 (Illumina) was used for library preparation, followed by sequencing on an Illumina HiSeq 2500.
- RNA-seq gene level count values were computed using the R package GenomicAlignments over aligned reads with UCSC KnownGene in hg19 as the base gene model.
- Differentially expressed gene (DEG) analysis were performed through the R package DESEq2. DEG analysis results were used as input for immune deconvolution analysis and Gene-set enrichment analysis (GSEA) against the Hallmark gene set collection from MSigDB, through the R package clusterProfiler.

Figuras



Resultados

- 5 distinct molecular clusters were identified based on the expression of the top 10% differentially expressed genes in the MSK100 cohort : C1: N=17; C2: N=18; C3: N=30; C4: N=11; C5: N=24. **(Fig. 1).**
- C1 & C2 were enriched with higher stage tumors (pT3 & pT4 = 58.8%, 72.2%, respectively), while C5 was the most enriched with non-invasive tumors (pTa & pT1 = 83.3%).
- The 5 transcriptionally-defined subsets of UTUC correlated with disease specific survival, with the C2 cluster showing the lowest DSS followed by C1 **(Fig. 2)**. Recurrence frequency was highest for C2 (77.8%) and C1 (47.1%) **(Fig. 3).**
- Basal/squamous, stroma-rich and neuroendocrine-like subtypes were enriched in patients who developed disease recurrence following surgery (8% vs. 14.29%, p = 0.056**) (Fig. 4).** C2 was particularly enriched for non-Luminal Papillary tumors (6/18).
- C1 & C2 showed high myeloid infiltration (including high Adenosine signaling and macrophages), Immune Score, APM2 (antigen presenting machinery 2) and CYT (cytolytic score) **(Fig. 5).** C2 & C3 had high levels of CD8T cells, with the deconvolved score being higher in C2 than C3.
- C1 & C2 were enriched with several Hallmark immune and inflammatory signatures (allograft rejection, inflammatory response, IL6 JAK/STAT3 signaling, and IL2 STAT5 signaling). C1 demonstrated a particularly inflamed phenotype, with additional enrichment of TNF-**α** signaling via NF-**κ**B, INF-**α** and INF-**γ** response gene sets **(Fig. 6).**

Conclusão

- We identified 5 transcriptionally distinct UTUC clusters **(Fig. 1)** that correlate with pathologic T-stage, recurrence frequency, and disease specific survival.
- C2 & C1 were associated with poorer prognosis: decreased disease specific survival **(Fig. 2)**, and higher incidence of recurrence **(Fig. 3).**
- Non-Luminal Papillary tumor subtypes were enriched in patients who developed recurrence **(Fig. 4)**, and in the C2 cluster.
- Patients with recurrence had higher levels of inflammatory markers, adenosine signaling, and macrophage infiltration, which were also enriched in C1 and C2. C1 displays a more inflamed phenotype while C2 exhibits higher CD8T cell infiltration **(Fig. 5 & 6)**.
- C1 followed by C2 had the highest scores for immunesuppresion and immunecheckpoints, expressing higher levels of PD1 and PDL1.
- Our future aims are to explore cluster relationship to response to treatment such as immunotherapy.

Referências

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