Abstract #6095

Comparative transcriptomic analysis identifies similarities and therapeutic vulnerabilities in Olfactory Neuroblastoma (ONB), Sinonasal Neuroendocrine Carcinoma (SNEC) and Sinonasal Undifferentiated Carcinoma (SNUC)

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Background

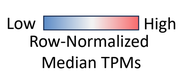
- ONB, SNEC and SNUC are rare sinonasal epithelial and neuroepithelial tumors for which there is no established systemic treatment standard of care for patients with recurrent/metastatic disease. Their rarity is an obstacle towards developing preclinical models and dedicated clinical trials.
- For ONB, transcriptomic similarities have been reported with glioblastoma, low-grade glioma, pheochromocytoma, paraganglioma, and more recently with small cell lung cancer (SCLC) [1,2]. Such studies are not available for SNUC and SNEC.
- We compared the transcriptomes of ONB, SNUC, SNEC, neuroendocrine (NE) and central nervous system tumor samples from a real-world (RW) patient cohort to identify similarities and uncover pharmacological vulnerabilities.

Methods

- Tumor specimens from patients with ONB (n=26), SNUC (n=9), SNEC (n=6), SCLC (n=1751), pancreatic NE tumors (PNET) (n=16), pheochromocytoma (n=23), paraganglioma (n=50), low grade glioma (n=657), glioblastoma (n=4524) and neuroblastoma (n=47) were tested by Caris Life Sciences, Phoenix, AZ.
- RNA sequencing (bulk) data were processed to obtain transcripts per million (TPM) values for downstream analysis.
- Clustering was performed with the 2000 highly variant genes. For tumor types with n>100, a random subset of 50 samples was used.
- ONB was subtyped by clustering to neural and basal [1,3].
- RW overall survival (rwOS) was calculated from insurance claims (tissue collection to last contact), compared with log-rank test; the Cox proportional hazards model was used for hazard ratio (HR).
- We examined the sinonasal tumors for expression of genes encoding for druggable surface molecules, including: *F3* (tissue factor), *PVRL4* (Nectin-4), *TACSTD2* (TROP2), *ERBB2* (HER2), *ERBB3* (HER3), *MET, EGFR, DLL3*, *PMEL* (gp100), *CLDN18* (Claudin-18), *GPC3* (Glypican-3), *CD276* (B7-H3), *VTCN1* (B7-H4), *FOLR1* (FRα).

- *Basal ONBs, SNUC and SNEC cluster with SCLC and pancreatic NETs.*
- *This cluster is associated with worse rwOS.*
- *Neural ONBs cluster independently.*
- *Expression of genes encoding for targetable surface proteins in ONB, SNUC and SNEC indicates presence of actionable subsets.*

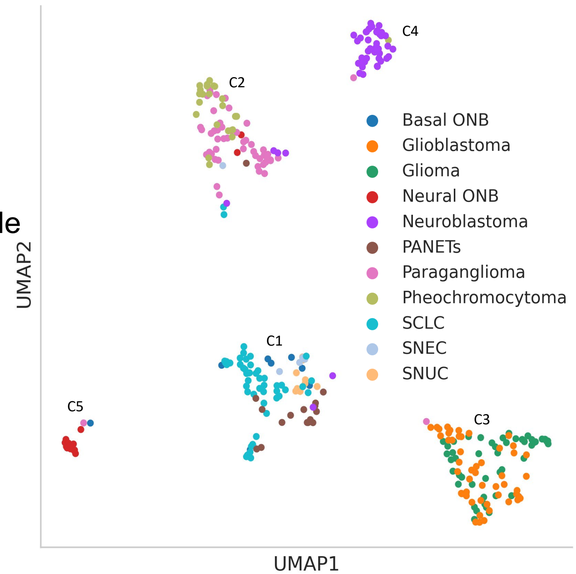
Results



- ONB had the highest expression for ***F3* (34.5** transcripts per million**)**, *CD276* (15.6), *GPC3* (7.2) and *CLDN18* (1.1);
- SNUC had the highest expression of ***ERBB2* (16.4),** *TACSTD2* (13.9), *EGFR* (9.2), *PVRL4* (6.2), *PMEL* (2.0) and *FOLR1* (1.5)
- SNEC had the highest expression of ***ERBB3* (83.3), *MET* (32.4),** *DLL3* (3.5) and *VTCN1* (1.7)

Results

- We identified 5 transcriptomic clusters (C1-C5, Fig 1).
- ONBs clustered separately from paragangliomas, pheochromocytomas, glioblastomas, low-grade gliomas, neuroblastomas.
- Basal ONBs clustered mostly with SNUC, SNEC, SCLC, PNETs (C1; associated with worse rwOS).
- Neural ONBs clustered separately (C5).



Future Directions for Research

We intend to perform further exploration of transcriptomic similarities and sub-clustering. We also plan to study the protein expression of selected druggable targets with high gene expression to validate our findings.

References

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