Single cell RNA-seq analysis of neuroendocrine tumors

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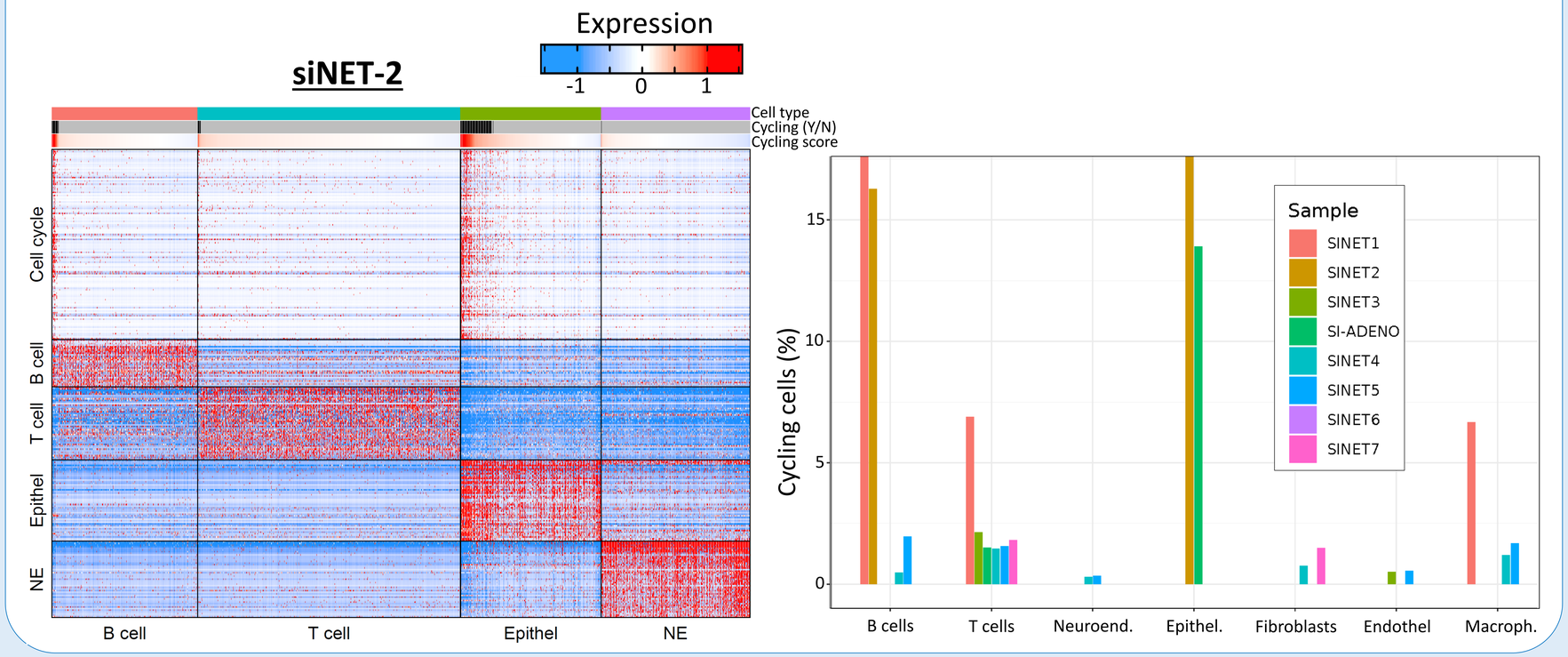
(1) Abstract

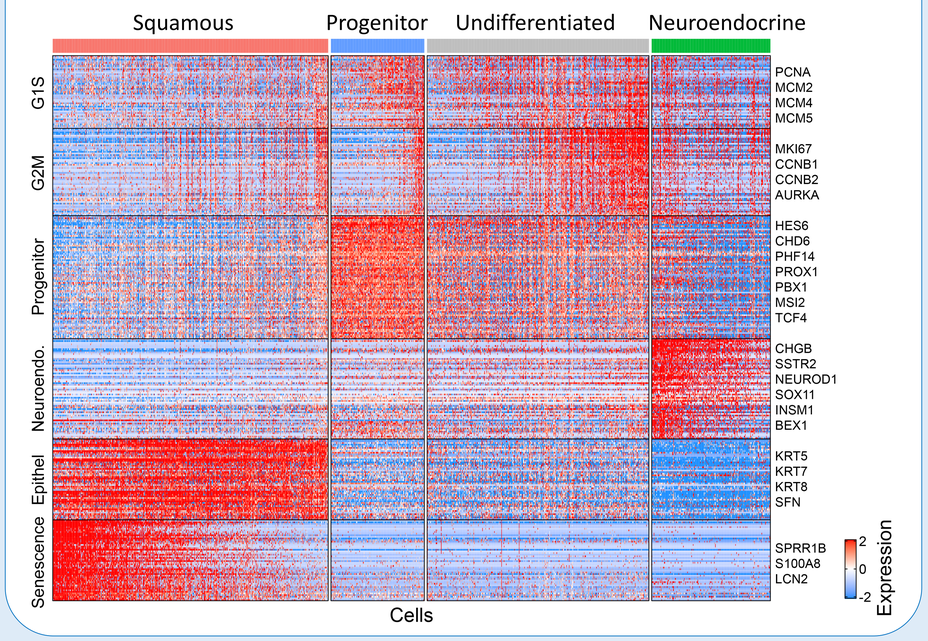
We are using single cell RNA-seq to comprehensively characterize the cellular diversity of neuroendocrine tumors (NETs).

- In low-grade siNETs, unlike in other cancers, we find that cancerous neuroendocrine (NE) cells primarily do not express the cell cycle program and therefore appear to be largely non-proliferative. In contrast, we find higher proliferation among other cell types, including epithelial cells, B cells and T cells, raising questions regarding the mode of growth of these tumors and the meaning of Ki67 clinical staining.
- In one case of large cell neuroendocrine carcinoma (LCNEC) combined with squamous cell carcinoma, we find high proliferation among undifferentiated cells that partially express both epithelial and neuroendocrine markers, consistent with the possibility that they drive the growth of the tumor while producing both NE and squamous cells.

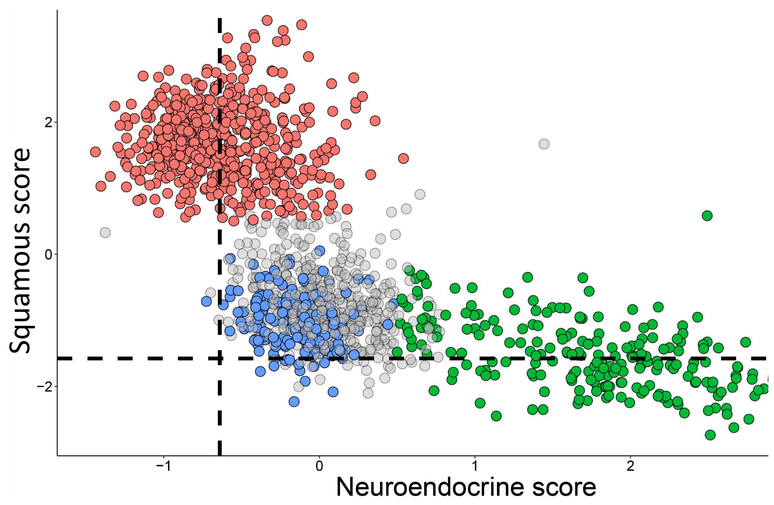
(2) Proliferating cells in small intestine NETs



(3) Proliferation of undifferentiated cells in LCNEC



(4) Undifferentiated cells partially express NE and epithelial programs



(5) Discussion

scRNA-seq of low-grade NETs suggest <1% in-vivo proliferation of NE cells and higher proliferation of epithelial cells and B cells.

Potential explanations:

1. Minimal NE proliferation (<1%) is still sufficient to initiate and maintain NETs
2. Spatial heterogeneity: NE cells proliferate in restricted areas, not captured by current data.
3. Epithelial-like cells function as progenitors of NE cells as suggested by a higher-grade mixed tumor.