Which cells are proliferating in neuroendocrine tumors?

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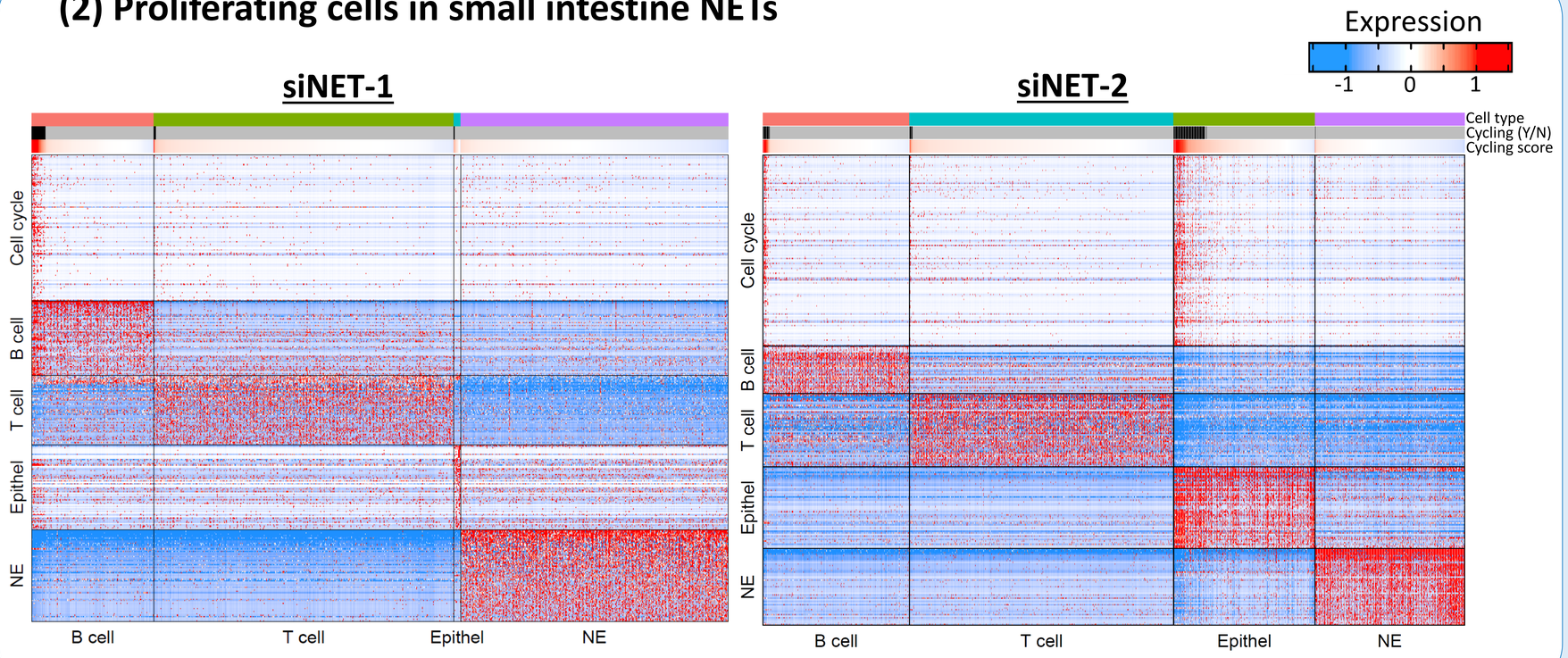
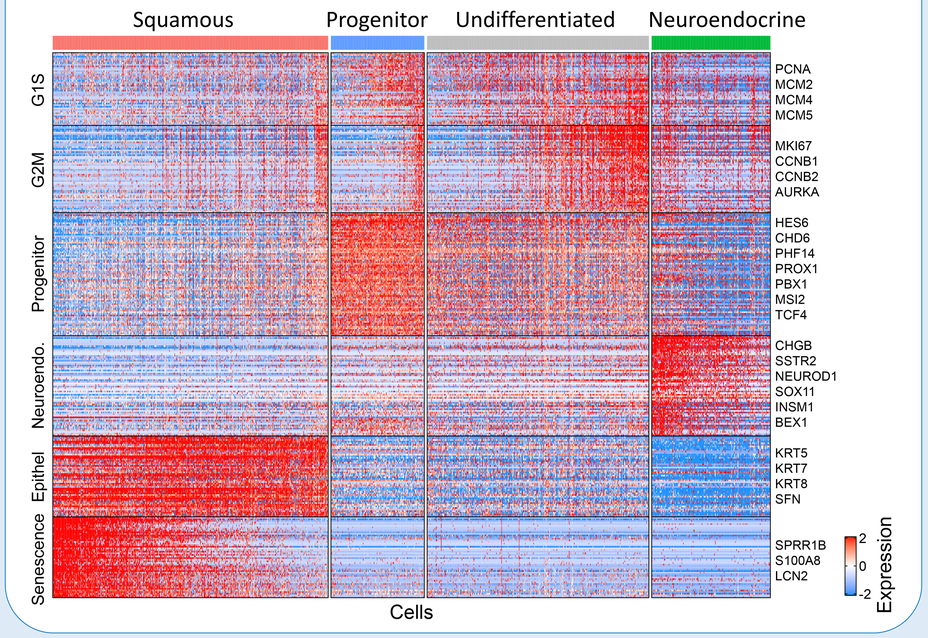
(1) Abstract

We are using single cell RNA-seq to comprehensively characterize the cellular diversity of neuroendocrine tumors (NETs). Unlike in other cancers, the presumed cancerous cells - the neuroendocrine (NE) cells - primarily do not express the cell cycle program and therefore appear to be non-proliferative. In contrast, we find higher proliferation among epithelial cells and in some case among B cells. 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 squmous cells. We speculate that proliferating epithelial cells may differentiate into NE cells also in low-grade NETs, but further analyses of the identity and plasticity of proliferating cells in NETs is needed to evaluate this hypothesis.

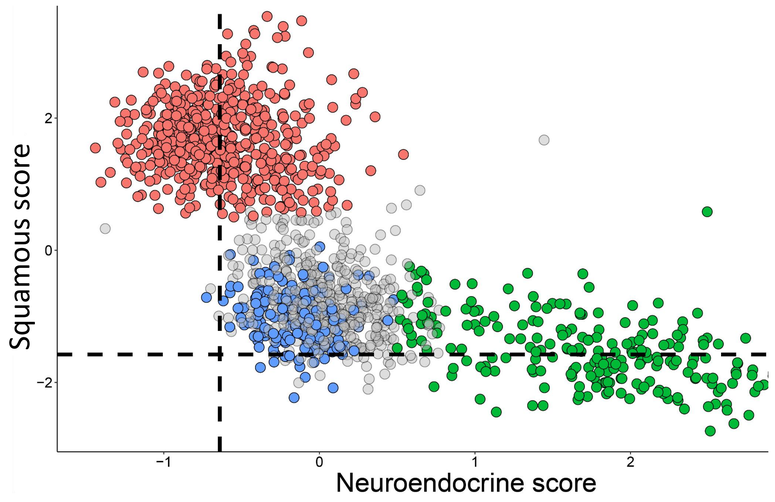
(2) Proliferating cells in small intestine NETs



(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.