Which cells are proliferating in neuroendocrine tumors?

Debdatta Halder[1], Avishay Spitzer[1], Chaya Barbolin, Moshe Biton[1], Amit Tirosh[2] and Itay Tirosh[1]

[1] Weizmann Institute of Science, Rehovot, Israel

[2] Sheba Medical Center, Ramat Gan, Israel

Neuroendocrine neoplasms (NENs) are complex tumors that remain poorly understood. To improve our understanding of their cellular composition and diversity, we profiled NEN patient samples by single cell RNA sequencing. Following optimizations and exclusion of low-quality datasets, we obtained comprehensive single cell data for 5 NENs, including three small-intestine, one pancreatic and one lung tumor, and we are continuously working to expand this dataset. Based on this available data, we observe that NENs have a rich microenvironment that includes four main cellular components - neuroendocrine, epithelial, immune (T-cell, B-cell and macrophage) and stromal (fibroblasts and endothelial cells). For each of those components, we find diversity within individual tumors, as well differences across tumors. For example, among the neuroendocrine cells, we find cellular diversity within an individual tumor with respect to metabolic, neural and stress-related expression programs. Across different tumors, we find marked differences in the degree and identity of proliferating cells. In the low-grade tumors, we do not observe proliferation of neuroendocrine cells but instead find aberrant proliferation of epithelial cells and lymphocytes, possibly reflecting the abnormal tumor microenvironment. In contrast, in a high-grade lung neuroendocrine tumor we find proliferation of both neuroendocrine and epithelial cells, as well as a population of proliferating cells that seem to reflect previously undescribed progenitor cells.