Deep spatial profiling of secondary brain tumors

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Background

Brain tumours include glioblastoma (GBM), representing around 50% of all primary brain malignancies in adults, and secondary brain tumors, also called brain metastasis (BrM), occuring much more frequently and representing about 90% of all brain malignancies. Most BrM arise from the skin (melanoma), lungs, or breast. BrM from upper gastrointestinal cancer (UGI-BrM), originating from pancreatobiliary and gastroesophageal cancer, has only been studied to a very limited extent. The prognosis for BrM patients remains dismal despite intensive therapy. There is a high medical need for new therapeutic options.

Beyond cancer cell-intrinsic mechanisms, the tumor microenvironment (TME), comprising stromal and immune cells, has become focus of intensive investigation in systemic as well as in central nervous system (CNS) tumors. The heterogeneous, immunosuppressive nature of the brain-metastatic microenvironment (b-MME) has been linked to therapeutic failure, and immune microenvironment signatures correlate with prognosis. The b-MME has a distinct composition, dominated by functionally diverse astrocytes and pro-tumorigenic macrophages that are ontogenically distinct, with exclusion of infiltrating lymphocytes. Features and characteristics of the brain-MME in UGI-BrM are essentially unkown.

Planned research project (example)

Aims

The aim of the current study is to apply spatial transcriptomics to characterize the immunological landscape secondary brain tumours originating from UGI cancer patients, elucidating causes for therapy resistance in these brain malignancies with a very dismal prognosis.

Materials

Ten secondary brain tumors of the UGI-BrM type will be studied. Also TME of the primary tumors that gave rise to the secondary brain tumors will be studied, for comparison of the cellular composition and cellular interaction of stromal cells in the brain MME vs. primary tumor TME.
We will construct two tissue microarrays (TMAs), each with 20 cores, from formalin-fixed, paraffin embedded (FFPE) tissue blocks. On sections from these TMAs, we will perform spatial transcriptomics with the Xenium platform (10x Genomics).

Methods

- Characterization of **surgical specimens** with UGI-BrM and primary tumors
- Construction of **tissue micro-arrays (TMAs)**
- **Xenium platform (10x Genomics)** for spatial transcriptomics, meaning:
  - **Single-cell resolution** – Localize RNA transcripts in individual cells
  - **Spatial context** - the native tissue architecture is retained
- **Imaging Mass Cytometry (IMC) –** Deep spatial profiling of around 40 proteins will possibly be be used as ancillary technique

Are you a student of **Biomedicine, Biology, Medicine, Molecular Biology, Computational Biomedicine,** or a related discipline?
Please contact us if you are interested in our research:
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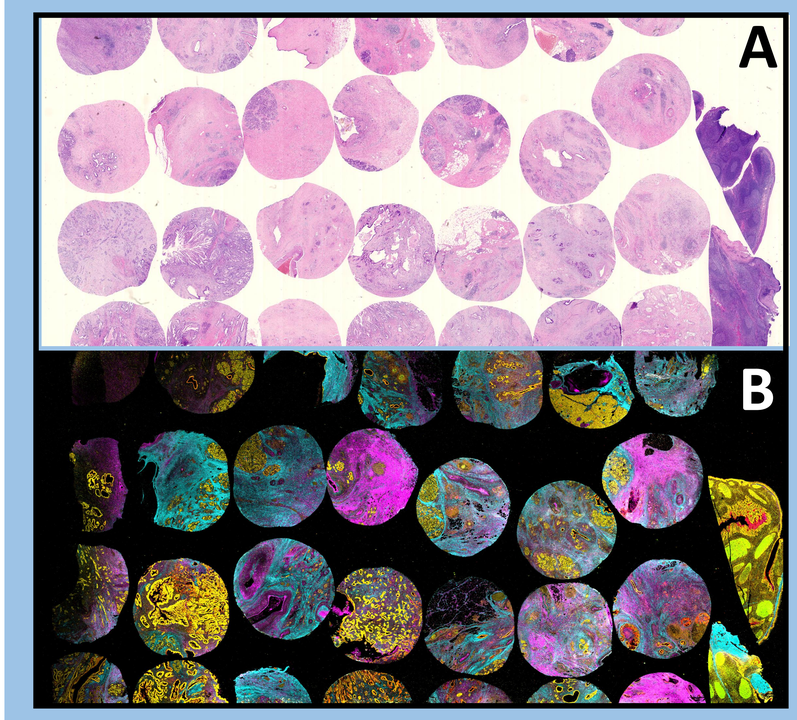

Figure 1. Tissue microarrays with cores from surgically treated pancreatic cancer.

A. H&E staining.

B. Deep spatial profiling (DSP) of TME using Imaging Mass Cytometry (Detlefsen et al. unpublished).

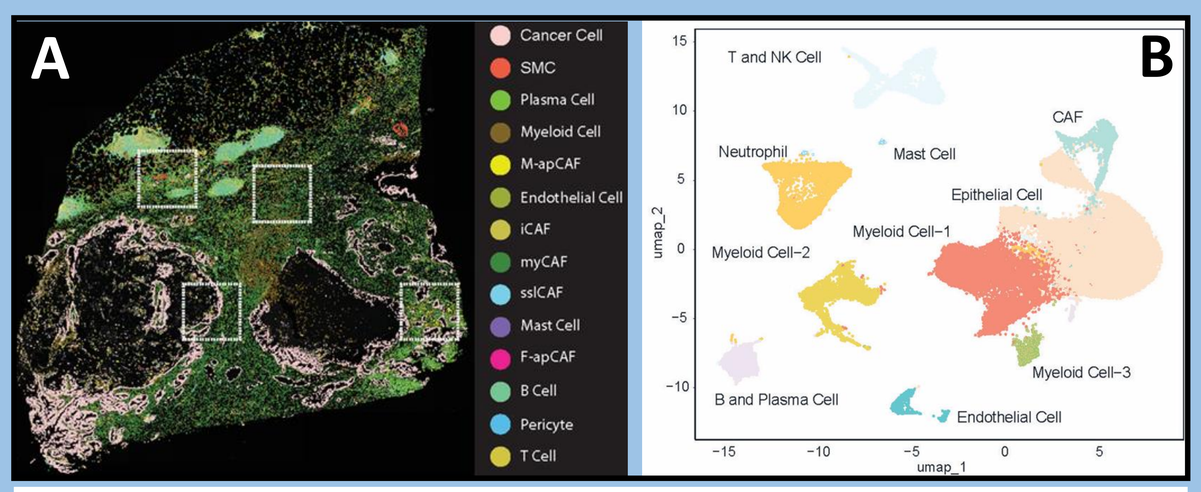

Figure 2. Single-cell spatial transcriptomics of pancreatic cancer. **A.** Spatial niches are computed by calculating the cell type composition of each cell using the k-nearest neighbor algorithm. **B.** Visualization of cellular components in four regions used for quantification (Chen et al. bioRxiv 2024. **doi:** https://doi.org/10.1101/2024.11.15.623232).

Examples of recent publications from Sönke Detlefsen's group

- **Detlefsen S**, Burton M, Ainsworth AP, …, Tarpgaard LS, Mortensen MB. RNA expression profiling of peritoneal metastasis from pancreatic cancer treated with systemic chemotherapy and PIPAC. *Pleura Peritoneum* 2024;9(2):79-91
- Ørbeck SV, Jakobsen T, García-Rodríguez JL, Burton M, Rasmussen LG, Ewald JD, Fristrup CW, Pfeiffer P, Mortensen MB, Kristensen LS, **Detlefsen S**. Exploring the prognostic value of circular RNAs in pancreatic ductal adenocarcinoma using genome-wide expression profiling. *Pancreatology* 2024;24(5):706-718
- Rasmussen LG, Verbeke CS, Sørensen MD, Pfeiffer P, Tan Q, Mortensen MB, Fristrup C, **Detlefsen S**. Gene expression profiling of morphologic subtypes of pancreatic ductal adenocarcinoma using surgical and EUS-FNB specimens. *Pancreatology* 2021 Apr;21(3):530-543