ETMR-05: Single-cell transcriptomics of ETMR reveals developmental cellular programs and tumor-pericyte communications in the microenvironment [Abstract]

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Angaben zur Veröffentlichung / Publication details:

Faria, Flavia W. de, Carolin Walter, Marta Interlandi, Viktoria Melcher, Nicole Riedel, Monika Graf, Natalia Moreno, et al. 2022. "ETMR-05: Single-cell transcriptomics of ETMR reveals developmental cellular programs and tumor-pericyte communications in the microenvironment [Abstract]." *Neuro-Oncology* 24 (Supplement 1): i50. https://doi.org/10.1093/neuonc/noac079.183.

ETMR-05. SINGLE-CELL TRANSCRIPTOMICS OF ETMR REVEALS DEVELOPMENTAL CELLULAR PROGRAMS AND TUMOR-PERICYTE COMMUNICATIONS IN THE MICROENVIRONMENT

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BACKGROUND: Embryonal tumors with multilayered rosettes (ETMR) are pediatric brain tumors bearing a grim prognosis, despite intensive multimodal therapeutic approaches. Insights into cellular heterogeneity and cellular communication of tumor cells with cells of the tumor microenvironment (TME), by applying single-cell (sc) techniques, potentially identify mechanisms of therapy resistance and target-directed treatment approaches. MATERIAL AND METHODS: To explore ETMR cell diversity, we used single-cell RNA sequencing (scRNA-seq) in human (n=2) and murine ETMR (transgenic mode; n=4) samples, spatial transcriptomics, 2D and 3D cultures (including co-cultures with TME cells), multiplex immunohistochemistry and drug screens. RESULTS: ETMR microenvironment is composed of tumor and non-tumor cell types. The ETMR malignant compartment harbour cells representing distinct transcriptional metaprograms, (NSC-like, NProg-like and Neuroblast-like), mirroring embryonic neurogenic cell states and fuelled by neurogenic pathways (WNT, SHH, Hippo). The ETMR TME is composed of oligodendrocyte and neuronal progenitor cells, neuroblasts, microglia, and pericytes. Tumor-specific ligand-receptor interaction analysis showed enrichment of intercellular communication between NProg-like ETMR cells and pericytes (PC). Functional network analyses reveal ETMR-PC interactions related to stem-cell signalling and extracellular matrix (ECM) organization, involving factors of the WNT, BMP, and CxCl12 networks. Results from ETMR-PC co-culture and spatial transcriptomics pointed to a pivotal role of pericytes in keeping ETMR in a germinal neurogenic state, enriched in stem-cell signalling. Drug screening considering cellular heterogeneity and cellular communication suggested novel therapeutic approaches. CONCLUSION: ETMR demonstrated diversity in the microenvironment, with enrichment of cell-cell communications with pericytes, supporting stem-cell signalling and interfering in the organization of the tumor extracellular matrix. Targeting ETMR-PC interactions might bring new opportunities for target-directed therapy.