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ID #605 FROM DIAGNOSIS TO RELAPSE: SINGLE-CELL AND SPATIAL MAPPING OF CELLULAR DEDIFFERENTIATION AND NICHE REMODELING IN PAIRED ETMR SAMPLES

Victoria Fincke^{1,2}, Nic Reitsam³, Lisa Siebenhüter³, Nina Jung³, Marlena Mucha^{4,2}, David Capper⁵, Cecilia Zuliani⁶, Philipp Sievers^{7,8}, Andreas Erbersdobler⁹, Arend Koch¹⁰, Matthias Schlesner¹¹, Bruno Märkl¹³, Dominik Sturm^{12,13,14,15,16,17}, Barbara von Zeitzschwitz¹⁸, Pascal Johann^{1,2}; ¹Pediatrics and Adolescent Medicine, Swabian Children's Cancer Center, University Hospital Augsburg, Augsburg, Germany, Augsburg, Bayern, Germany; ²Bavarian Cancer Research Center (BZKF), Bayern, Germany; ³University Hospital Augsburg, Institute for Pathology and digital medicine, Augsburg, Bayern, Germany; ⁴University Hospital Augsburg, Pediatrics and Adolescent Medicine, Swabian Children's Cancer Center, Augsburg, Bayern, Germany; ⁵Charite, Neuropathology, Berlin, Germany; ⁶Hopp Children's Cancer Center Heidelberg (KiTZ), Heidelberg, Baden-Württemberg, Germany; ⁷University of Heidelberg, University of Heidelberg, Mannheim, Germany; ⁸DKFZ, Heidelberg, Germany; ⁹Medical Faculty, University Rostock, Pathology, Rostock, Mecklenburg-Vorpommern, Germany; ¹⁰Charite, Neuropathology, Berlin, Berlin, Germany; ¹¹University Augsburg, Faculty of Applied Computer Sciences, Biomedical Informatics, Data Mining and Data Analytics, Augsburg, Bayern, Germany; ¹²Hopp Children's Cancer Center (KiTZ) Heidelberg, Pediatric Glioma Research (B360), Baden-Württemberg, Germany; ¹³Hopp Children's Cancer Center Heidelberg (KiTZ), Baden-Württemberg, Germany; ¹⁴Division of Pediatric Glioma Research, German Cancer Consortium (DKTK), German Cancer Research Center (DKFZ), Heidelberg, Baden-Württemberg, Germany; ¹⁵Heidelberg University, Heidelberg Faculty of Medicine, Department of Pediatric Oncology, Hematology and Immunology, Heidelberg University Hospital, Germany, Baden-Württemberg, Germany; ¹⁶Division of Pediatric Neurooncology, German Cancer Research Center (DKFZ) and German Cancer Consortium (DKTK), Heidelberg, Germany, Baden-Württemberg, Germany; ¹⁷Hopp Children's Cancer Center Heidelberg (KiTZ), Heidelberg, Germany, Baden-Württemberg, Germany; ¹⁸Charite University Hospital Berlin, Department of Pediatric Oncology and Haematology, Berlin, Germany

Embryonal tumors with multilayered rosettes (ETMR) are highly aggressive brain tumors predominantly affecting children under three years, with median survival of 10–14 months. Understanding mechanisms driving treatment resistance remains critical for improving outcomes. While the cell populations constituting primary tumors have been characterized in the recent years, the molecular landscape at relapse remains elusive.

We performed single-cell transcriptomic analysis of 20 samples from 13 patients with ETMR, with a particular focus on seven patients with matched tissue from primary and recurrent/progressive disease. Tumor populations comprised neural stem cell (NSC)-like cells (*SOX2+*, *SOX3+*), neuronal progenitor-like cells (*TCF4+*, *NEUROD1+*), and neuron-like cells (*TUBB3+*, *NEUROD4+*), consistent with previous reports. However, cellular composition shifted dramatically during progression: neuron-like cells decreased from ~45% in primary tumors to 25% in progressive disease and 10% at relapse, while NSC-like cells expanded to 57% in recurrent tumors.

Differential gene expression analysis revealed that relapse-associated NSC-like cells lost neuronal maturation programs while acquiring mesenchymal, HOX-driven, and stem-like characteristics. Significantly upregulated genes included HOX family members, epithelial-mesenchymal transition mediators (*COL1A1*, *MMP2*), and developmental regulators (*IRX5*, *HAND2*), while neuronal function genes (*OTX3*, *SPON1*) were downregulated. Critically, C19MC-amplified NSC-like cells were enriched at relapse while chromosome 2 gain variants decreased, suggesting C19MC amplification drives stem-like populations that dominate recurrent disease.

The microenvironment also transformed substantially: relapsed tumors exhibited 3–5 fold increases in infiltrating immune cells, pericytes, and astrocytes

compared to minimal tumor microenvironment in primary samples, suggesting more invasive growth patterns. Spatial transcriptomics (Xenium) at single-cell resolution validated these changes and revealed functionally distinct niches where tumor cells interact differentially with stromal compartments.

These findings demonstrate that ETMR progression involves coordinated dedifferentiation toward aggressive stem-like states and highlight potential applicability of immunotherapeutic approaches in the relapse setting.