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EPCO-37. DISSECTING GBM EVOLUTION FOLLOWING STANDARD-OF-CARE BY LARGE-SCALE LONGITUDINAL SINGLE NUCLEUS RNA-SEQUENCING

Masashi Nomura[1], Avishay Spitzer[2], Kevin Johnson[3], Luciano Garofano[4], Djamel Nehar-Belaid[5], Young Taek Oh[4], Kevin J Anderson[5], Ryan D. Najac[6], Lillian Bussema[7], Frederick Varn[5], Fulvio D'Angelo[4], Tamrin Chowdhury[8], Simona Migliozzi[4], Jong Bae Park[9], Luca Ermini[10], Anna Golebiewska[10], Simone Niclou[10], Sunit Das[11], Sun Ha Paek[12], Hyo-Eun Moon[12], Bertrand Mathon[13], Anna-Luisa Di Stefano[13], Franck Bielle[14], Alice Laurenge[13], Marc Sanson[14], Shota Tanaka[15], Nobuhito Saito[15], Steve Keir[16], David Ashley[17], Jason Huse[18], W.K. Alfred Yung[19], Anna Lasorella[4], Antonio Iavarone[20], Roel Verhaak[3], Mario Suva[7], and Itay Tirosh[2]; [1]Massachusetts General Hospital and Harvard Medical School, Boston, USA, [2]Weizmann Institute of Science, Rehovot, Israel, [3]Yale University School of Medicine, New Haven, CT, USA, [4]University of Miami, Coral Gables, USA, [5]The Jackson Laboratory, Bar Harbor, USA, [6]Columbia University, New York, USA, [7]Massachusetts General Hospital and Harvard Medical School, Boston, MA, USA, [8]Yale University School of Medicine, New Haven, USA, [9]National Cancer Center in Korea, Seoul, Republic of Korea, [10]Neuro-Oncology Laboratory - Luxembourg Institute of Health, Strassen, Luxembourg, [11]Unity Health Toronto, St. Michael's Hospital, Toronto, Canada, [12]Seoul National University, Seoul, Republic of Korea, [13]Pitie-Salpetriere Hospital, Paris, France, [14]Pitie Salpetriere Hospital, Paris, France, [15]The University of Tokyo Hospital, Tokyo, Japan, [16]Duke University School of Medicine, Durham, USA, [17]The Preston Robert Tisch Brain Tumor Center, Durham, USA, [18]University of Texas MD Anderson Cancer Center, Houston, TX, USA, [19]University of Texas MD Anderson Cancer Center, Houston, USA, [20]University of Miami, Miami, USA

The heterogeneity within tumors has long been associated with therapy failure and disease progression. Recent advances in single-cell RNA-sequencing technologies have enabled us to dissect the cellular diversity in glioblastoma (GBM). However, how these cellular programs change longitudinally under therapy remains poorly understood. To address this question, we collected and profiled a large-scale longitudinal cohort of 59 matched IDH-wildtype GBM sample pairs provided by 7 centers worldwide by single-nucleus RNA-sequencing (snRNA-seq) and whole-exome/whole-genome sequencing. The majority of patients (51 patients) in this cohort received standard-of-care (temozolomide and radiation) following initial tumor resection. Leveraging this large-scale snRNS-seq dataset of 457,442 cells, we detected novel cellular states and associations between malignant and tumor microenvironment (TME) cells, and then performed longitudinal analyses. The recurrent samples showed significantly lower malignant cell fraction (p=0.002) and reciprocal increase in proportions of glio-neuronal TME cell types (oligodendrocytes, neurons and astrocytes). The TME composition, malignant cell state proportions and baseline expression programs were retained at recurrence more than expected by chance, but overall were not well conserved between primary and recurrent samples. A subset of pairs (12/59 pairs) enriched with glio-neuronal TME at recurrence showed a significant transcriptomic shift and was associated with better clinical course (p=0.02). The tumors that acquired radiation-related small deletion phenotype underwent a transition towards MES/Hypoxia phenotype (0/9 at primary, 6/9 at recurrence, p=0.02). We defined pairs as likely responders or non-responders to treatment based on the MGMT methylation status of the primary tumor sample. This uncovered diverging evolutionary trajectories in cellular programs between the two groups. Strikingly, the changes in malignant state frequency and baseline malignant expression profile were strongly associated with specific changes in the TME composition. Our findings based on high-resolution longitudinal snRNA-seq analyses highlight the diverse evolutionary trajectories in GBM that are shaped by TME changes and treatments.