CSIG-04. INTEGRATED MOLECULAR AND FUNCTIONAL CHARACTERIZATION OF THE INTRINSIC APOPTOTIC MACHINERY IDENTIFIES A DIAGNOSTICALLY INFORMED THERAPEUTIC APPROACH FOR MALIGNANT GLIOMA

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Molecular profiling often fails to predict therapeutic outcomes in cancer. This failure is, in part, due to myriad of genetic alterations and the plasticity of cancer signaling networks. Functional profiling, which ascertains signaling dynamics, has emerged as an alternative method to anticipate drug responses. Here we performed combined molecular and functional characterization (via BH3 profiling) of the intrinsic apoptotic machinery in glioma patient samples and derivative models. We identified that standard of care treatment rewires the apoptotic machinery in a genotype specific manner, revealing targetable vulnerabilities in gliomas containing specific molecular features (e.g., TP53 WT). However, integration of BH3 profiling uncovered that high mitochondria priming was also required to induce tumor apoptosis. Accordingly, a composite molecular and functional signature best predicted responses of diverse intracranial glioma models to standard of care combined with a new clinical drug targeting the intrinsic apoptotic machinery. This work demonstrates how complementary functional and molecular data can robustly predict therapy-induced cell death.