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Modulating native GABAA receptors in medulloblastoma with positive allosteric benzodiazepine-derivatives induces cell death

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The pediatric brain cancer medulloblastoma is comprised of four molecular subgroups. Group 3 subgroup medulloblastoma patients have the highest rates of relapse and metastasis and a 20% survival rate after standard-of-care. Our analysis of gene expression of 763 medulloblastoma tumors reveals that group 3 patient tumors share high subgroup-specific and correlative expression of *GABR* genes *GABRA5*, *GABRB3* and *GABRG2* and 3, which code for α5, β3 and γ2 and 3 subunits, respectively, of the ionotropic γ-aminobutyric acid type A receptor ($GABA_AR$). There are approximately 1000 functional α5-$GABA_ARs$ per cell in the group 3 patient-derived cell line D283 that mediate a basal chloride-anion flux of $2x10^9$ ions/sec. Benzodiazepines, designed to function as α5-$GABA_AR$ preferring positive allosteric modulators with psychotropic activity, can impair the viability of group 3 cells by enhancing α5-$GABA_AR$ chloride-anion flux and subtle changes in benzodiazepine structure has significant impact on potency. A particularly potent α5-$GABA_AR$ preferring benzodiazepine ('KRM-II-08') that emerged from our screen and shown to be non-toxic, binds to the native α5-$GABA_AR$ with IC_{50} and EC_{50} of 0.8 μM. This benzodiazepine enhances a chloride-anion flux that induces within minutes, mitochondrial membrane depolarization and fragmentation. In response, *TP53* is upregulated and p53, constitutively phosphorylated at S392, localizes to the cytoplasm. This correlates with localization of pro-apoptotic Bcl-2-associated death promoter (BAD) protein. *GABR* expression can serve as a diagnostic biomarker for group 3 tumors, while α5-$GABA_AR$ is a therapeutic target for benzodiazepine binding, which enhances an ionic imbalance in group 3 cells that perturbs mitochondrial function and induces a response that results in apoptosis.

Biography

Soma Sengupta is a clinician-scientist, board certified in neurology and neuro-oncology, trained at the University of Cambridge (UK) and the Harvard hospitals (Boston, MA, USA). She is actively involved in caring for patients with brain cancers at the Winship Cancer Institute, Emory University. She initiates and participates in clinical trials, and runs a translational neuro-oncology laboratory to develop targeted therapeutic strategies to treat brain cancers as well as cancers outside the central nervous system.

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