

GABRA5

Gamma-aminobutyric acid (GABA) A receptor, alpha 5, also known as GABRA5, is a protein which in humans is encoded by the GABRA5 gene.

GABA is the major inhibitory neurotransmitter in the mammalian brain where it acts at GABAA receptors, which are ligand-gated chloride channels. Chloride conductance of these channels can be modulated by agents such as benzodiazepines that bind to the GABAA receptor. At least 16 distinct subunits of GABAA receptors have been identified. Transcript variants utilizing three different alternative non-coding first exons have been described.

Recent research has produced several ligands which are moderately selective for GABAA receptors containing the $\alpha 5$ subunit. These have proved to be useful in investigating some of the side effects of benzodiazepine and nonbenzodiazepine drugs, particularly the effects on learning and memory such as anterograde amnesia. Inverse agonists at this subunit have nootropic effects and may be useful for the treatment of cognitive disorders such as Alzheimer's disease.

Group 3 medulloblastomas are characterized by frequent amplifications of the oncogene [MYC](#), a high incidence of [metastasis](#), and poor [prognosis](#) despite aggressive [therapy](#).

Group 3 molecular subgroup patients have the highest [relapse](#) rates and after standard-of-care have a 20% [survival](#). Group 3 tumors have high expression of [GABRA5](#), which codes for the $\alpha 5$ subunit of the γ -aminobutyric acid type A receptor (GABAAR).

Kallay et al., performed analysis of GABR and MYC expression in MB tumors and used molecular, cell biological, and whole-cell electrophysiology approaches to establish presence of a functional 'druggable' GABAAR in group 3 cells.

Analysis of expression of 763 MB tumors reveals that group 3 tumors share high subgroup-specific and correlative expression of GABR genes, which code for GABAAR subunits $\alpha 5$, $\beta 3$ and $\gamma 2$ and 3. There are ~ 1000 functional $\alpha 5$ -GABAARs per group 3 patient-derived cell that mediate a basal chloride-anion efflux of 2×10^9 ions/s. Benzodiazepines, designed to prefer $\alpha 5$ -GABAAR, impair group 3 cell viability by enhancing chloride-anion efflux with subtle changes in their structure having significant impact on potency. A potent, non-toxic benzodiazepine ('KRM-II-08') binds to the $\alpha 5$ -GABAAR (0.8 μ M EC50) enhancing a chloride-anion efflux that induces mitochondrial membrane depolarization and in response, TP53 upregulation and p53, constitutively phosphorylated at S392, cytoplasmic localization. This correlates with pro-apoptotic Bcl-2-associated death promoter protein localization.

GABRA5 expression can serve as a diagnostic biomarker for group 3 tumors, while $\alpha 5$ -GABAAR is a therapeutic target for benzodiazepine binding, enhancing an ion imbalance that induces apoptosis ¹⁾.

¹⁾

Kallay L, Keskin H, Ross A, Rupji M, Moody OA, Wang X, Li G, Ahmed T, Rashid F, Stephen MR, Cottrill KA, Nuckols TA, Xu M, Martinson DE, Tranchese F, Pei Y, Cook JM, Kowalski J, Taylor MD, Jenkins A, Pomeranz Krummel DA, Sengupta S. Modulating native GABA(A) receptors in medulloblastoma with positive allosteric benzodiazepine-derivatives induces cell death. J Neurooncol. 2019 Feb 6. doi: 10.1007/s11060-019-03115-0. [Epub ahead of print] PubMed PMID: 30725256.

From:

<https://neurosurgerywiki.com/wiki/> - **Neurosurgery Wiki**

Permanent link:

<https://neurosurgerywiki.com/wiki/doku.php?id=gabra5>

Last update: **2024/06/07 02:54**

