Could $\alpha 5$ -GABA-A receptor activation be used as a target for managing medulloblastomas?

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‘Medulloblastoma cerebelli’ was initially described by Cushing and Bailey in 1925 [1]. Medulloblastomas are the most common malignant brain tumors in children and are a significant cause of cancer-related deaths in children [2]. Since their initial description, enormous headway has been made in the molecular characterization of this highly malignant predominantly pediatric brain tumor [3–6].

Recent genomic studies have delineated the molecular heterogeneity of these tumors. They are now classified into subtypes, each with a unique molecular signature and clinical outcome: SHH, WNT, group 3 and group 4 [3–6]. Interestingly, patients with group 3 medulloblastomas have a worse prognosis compared with the other medulloblastoma subtypes [7]. Indeed, 5-year progression-free survival is less than 20% for group 3 medulloblastomas after maximal therapy with external-beam radiation and multidrug chemotherapy, as compared with 70% 5-year progression-free survival for all other

medulloblastoma subtypes. Ten years after disease onset, almost all group 3 medulloblastoma patients will have succumbed to the disease. Therefore, it is of paramount importance to develop effective targeted therapy to manage this subtype of patients. Group 3 medulloblastomas are characterized by oncogenic *MYC* signaling, often through a high level of *MYC* amplification. In terms of the current arsenal of chemotherapeutic regimens and radiotherapy, this makes this subtype of medulloblastoma particularly resistant to standard chemotherapy. Unfortunately, attempts at developing drugs that target the *MYC* protein in group 3 medulloblastomas have so far been unsuccessful.

Gene-expression profiling revealed an enrichment of genes associated with GABA pathway signaling in *MYC*-driven/group 3 medulloblastomas, largely from increased *GABRA5* expression [3]. *GABRA5* encodes the $\alpha 5$ subunit of the GABA-A receptor complex. This appears to be unique to the group 3 medulloblastomas. This receptor

KEYWORDS

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complex is composed of two α -, two β - and one γ -subunit. These receptors function primarily as ligand-gated chloride channels, which bind to GABA, other endogenous peptides and a host of pharmacological agents at defined sites around/within the receptor complex [8]. Binding specificity is mediated in part by the existence of multiple α_{1-6} , β_{1-3} and γ_{1-2} subunits, which are also temporally and spatially dynamic. The most ubiquitous and abundant GABA-A receptor complexes in the CNS contain α_1 subunits [9], while α_5 subunit-containing GABA-A receptors are more restricted in their expression with the highest levels noted in distinct sets of neurons in the hippocampus, cerebellum and sensory-related brain regions [10]. Of note, GABA-A receptor signaling is excitatory only in early development, otherwise it causes inhibitory neurotransmission [11]. In addition, Andang *et al.* [12] showed elegantly that the GABA signaling pathway acts as a critical housekeeping regulator of stem cell maintenance, and it does so by a γ -H2AX dependent fashion. Interestingly, histone deacetylase (HDAC) inhibitors also operate by a similar mechanism [13]. Indeed, Wechsler-Reya's group has data to suggest that HDAC inhibitors are able to kill group 3 medulloblastoma cells *in vitro* and *in vivo*. Thus, a new area of interest is to use GABRA5 receptor agonists with HDAC inhibitors to see whether these act synergistically.

GABA-A receptors have a diverse repertoire of small molecules that can modulate the receptor activity, such as benzodiazepines, many of these derivatives are US FDA approved as antiseizure medications, anxiolytics and anesthetics. Cook, our collaborator [14], supplied us with pure agonists, inverse agonists, antagonists, allosteric modulators (positive and negative) against GABRA5. These compounds were originally developed for psychiatric indications, such as alcohol dependence. Our rationale for using these compounds was that if we were able to modulate GABRA5 activity, then group 3 medulloblastoma survival could potentially be modulated. Our work demonstrated that targeting GABRA5 using an α_5 -specific agonist,

QH-ii-066 resulted in decreased group 3 medulloblastoma cell viability, and sensitization of these cells to cisplatin, vincristine and γ -radiation. Further work suggested that these effects are modulated by inducing HOXA5, resulting in an upregulation of p53. In our work, QH-ii-066 activates GABRA5, and we hypothesize that this causes global effects on MYC and p53 [13]. There is potential to extrapolate this paradigm to other cancers where GABRA5 signaling seems to be implicated, including neuroblastoma [15], and squamous cell lung cancer [16]. More studies need to be carried out to see whether GABRA5 or players in its signaling pathway can be utilized as novel drug targets. Another theory may be that the upregulation of GABRA5 expression in group 3 medulloblastomas may simply be a ‘bystander’ effect. However, further experiments need to be carried out to elucidate the exact role of GABRA5 in this subtype of medulloblastomas. Finally, since GABRA5 is expressed in the dentate gyrus of the adult mouse, further animal work will need to be carried out to make sure that GABRA5 agonists do not cause any cognitive issues both in the developing and mature brain [17].

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