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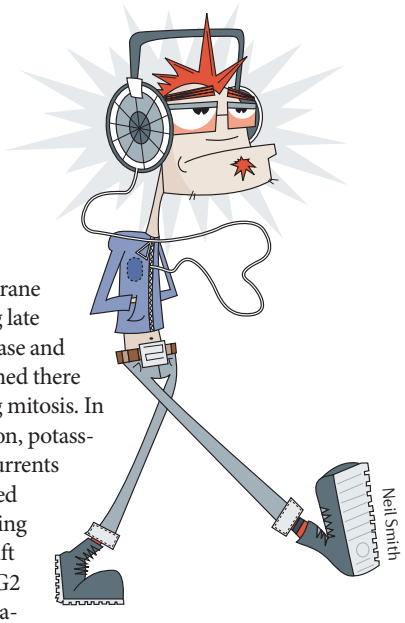
MEDULLOBLASTOMA

Pump up the volume



Although progress has been made in the genetic and molecular characterization of medulloblastoma, this aggressive tumour type is not easily treated, and patients often experience relapse or impaired quality of life following treatment. It is therefore of interest to identify new molecular pathways controlling medulloblastoma growth and progression that might be amenable to therapy.

Lily Jan, Xi Huang and colleagues investigated the role of ion channels in medulloblastoma by analysing microarray data from two medulloblastoma mouse models. The voltage-gated potassium channel *Eag2* (also known as *Kcnh5*) was highly upregulated in tumour tissue compared with normal adult cerebellum, and the authors validated both increased mRNA and protein levels of EAG2 using several methods. High EAG2 protein levels were also observed in human medulloblastoma xenografts, and EAG2 mRNA and protein were significantly increased in a large proportion of primary human medulloblastomas of different molecular subtypes.

Does EAG2 have a role in tumorigenesis? Knockdown of *EAG2* by RNA interference — in cells established from a patient with medulloblastoma that highly expressed EAG2, and in mouse medulloblastoma cells — inhibited proliferation and induced apoptosis, indicating that EAG2 expression can confer a growth advantage. In xenograft tumours, EAG2 knockdown slowed tumour growth and prevented metastatic spread, leading to significantly increased survival of the mice.

To investigate how EAG2 affects cell growth, the authors first showed that EAG2 operated as a functional potassium channel in freshly isolated medulloblastoma cells from mice, as measured by whole-cell voltage clamp recordings. They then examined the cellular localization of the protein: EAG2 was mostly intracellular during interphase, but shuttled to the plasma membrane during late G2 phase and remained there during mitosis. In addition, potassium currents changed following the shift in EAG2 localization. EAG2 knockdown increased the proportion of medulloblastoma cells in late G2 phase, and decreased those in each phase of mitosis (no change in the number of cells in G1 or S phase was observed), indicating that EAG2 is required for cells to enter mitosis. Mitotic entry is typically accompanied by a reduction in cell volume (premitotic cytoplasmic condensation); both this and mitotic morphology were abnormal in medulloblastoma cells lacking EAG2. Downstream of EAG2, p38 MAPK was activated both in medulloblastoma cells *in vitro* and in xenograft tumours, and inhibition of p38 rescued the growth of medulloblastoma cells with EAG2 knockdown.

> “EAG2 expression can confer a growth advantage”

Overexpression of EAG2 in non-tumour cells enhanced its membrane localization throughout the cell cycle; this promoted a reduction in cell volume and a mitotic-like morphology even in cells in interphase, leading to decreased cell growth. Although this may seem counterintuitive given the overexpression of EAG2 in tumour cells, the authors propose that the correct subcellular localization of EAG2 is crucial for promoting growth.

Ion channels are highly druggable, and it will be interesting to see whether inhibition of EAG2 can be used therapeutically in medulloblastoma.

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ORIGINAL RESEARCH PAPER Huang, X. *et al.* Voltage-gated potassium channel EAG2 controls mitotic entry and tumor growth in medulloblastoma via regulating cell volume dynamics. *Genes Dev.* 1 Aug 2012 (doi:10.1101/gad.193789.112)