News & views

Cancer

A neuronal trigger for cancer in mice

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Light-induced activation of neuronal cells in the retina stimulates the formation of optic-nerve tumours in cancer-prone mice, revealing a potential role of neuronal activity in cancer initiation. **See p.277**

Cancer is not a disease involving uncontrolled division of isolated cells; rather, it is a condition in which various types of normal and malignant cells collaborate to drive tumour growth and dissemination. To the surprise of many, the nervous system — which includes neuronal cells and non-neuronal cells of the brain, spinal cord and nerves throughout the body — can also be involved in cancer progression. Pan *et al.*[1] report on page 277 that, in a mouse model of a rare disease that predisposes people to tumours along the optic nerve, light-induced neuronal activity is responsible not only for the growth of these tumours, but also for their initiation.

Neurofibromatosis type 1 (NF1) affects one in about 3,000 people worldwide, and is caused by a mutation in the gene of the same name. Individuals with the *NF1* gene mutation are predisposed to early-childhood development of slow-growing (low-grade) tumours called gliomas along the optic pathway — the nervous pathway that includes the optic nerve and that carries visual information from the light-sensing cells of the retina to the brain.

The starting point for Pan and colleagues' study was a mouse model in which nearly all cells in the body carry the mutation in the mouse *Nf1* gene, but in which only the cells that transform into optic pathway gliomas (neural progenitor cells) lack a functional copy of the *Nf1* gene completely[2]. Both of these conditions are a prerequisite for the development of optic pathway gliomas in mice at a young age (by about nine weeks)[3], reflecting the situation in children and young adults with NF1, who can develop gliomas that show a lack of NF1 expression. Pan *et al.* used this relatively simple and controllable mouse model — called the *Nf1*–optical pathway glioma ($Nf1^{OPG}$) model — to address the exciting question of whether exposure to light, which increases neuronal activity in the optic pathway, triggers the formation of optic pathway gliomas.

The authors tested whether raising young $Nf1^{OPG}$ mice in the dark from 6 to 12 weeks of age prevented the formation of optic pathway gliomas. Remarkably, it did. Moreover, placing $Nf1^{OPG}$ mice with already initiated tumours in darkness later in life (from 12 to 16 weeks) strongly reduced tumour growth. In line with these findings, artificial activation of neurons in the optic nerve, using a technique called optogenetics, drove increased growth of optic pathway gliomas in $Nf1^{OPG}$ mice.

Next, the authors explored the molecular determinants behind the effects of visual experience on glioma growth (Fig. 1). In previous studies of another type of brain tumour (aggressive high-grade glioma), some researchers from the study by Pan *et al.* demonstrated that activated neurons secrete a protein called brain-derived neurotrophic factor and shed another protein, called neuroligin-3, that in turn stimulates glioma growth[4]. In Pan and colleagues' study, the team found that optogenetic stimulation of neurons in the retina increased the levels of both factors in the optic pathway, and that both proteins promoted the proliferation of low-grade glioma cells in culture. The role of neuroligin-3 in driving tumour growth in the $Nf1^{OPG}$ model was then confirmed by demonstrating that its genetic loss from these mice, like light deprivation, reduced the incidence of glioma.

Pan *et al.* also detected high levels of neuroligin-3 in tumour samples from humans with a type of low-grade glioma related to optic pathway gliomas, called pilocytic astrocytomas, although the level of expression varied

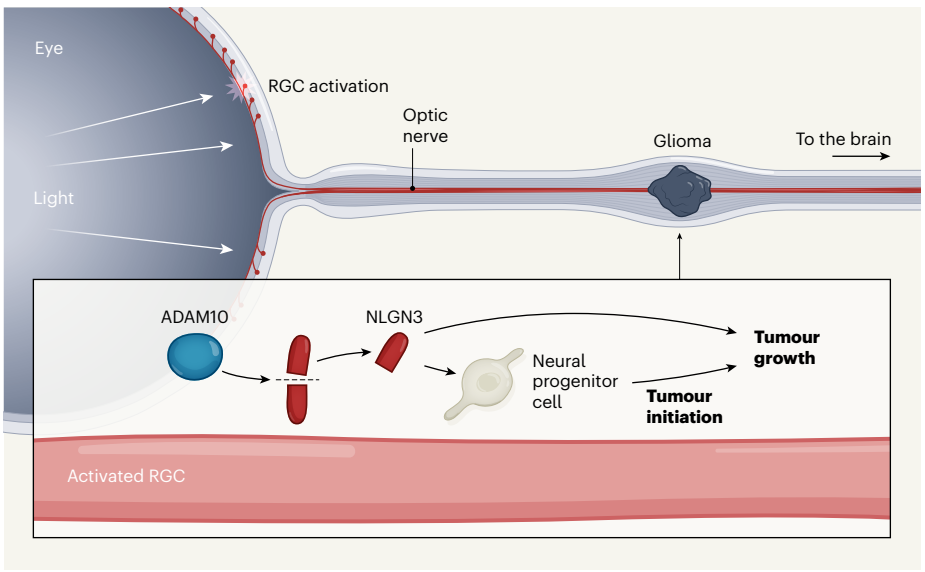

Figure 1 | Neuronal activity in the optic nerve of susceptible mice drives tumour formation. Neurofibromatosis type 1 (NF1) is a syndrome in which people are prone to developing certain types of cancer. Pan *et al.*[1] report that, in a genetically engineered mouse model of NF1, the light-induced activation of retinal ganglion cells (RGCs) is sufficient to induce the formation of tumours called gliomas of the optic nerve that contains a bundle of RGC projections carrying visual information to the brain. Compared with what happens in regular mice, activated RGCs in the model mice release more of the protein neuroligin-3 (NLGN3), which is cleaved from the cell membrane (not shown) by the enzyme ADAM10. NLGN3 promotes the transformation of neural progenitor cells into tumour cells, giving rise to optic pathway gliomas, and also stimulates the growth of these tumours.

between samples. Notably, tumour samples showing particularly high expression of neuroligin-3 also exhibited high expression of genes associated with the formation of synapses, the connections between neurons. This finding raises the question of whether neuron–glioma synapses that have been found in high-grade gliomas, where they boost tumour aggressiveness[5,6], are also present in NF1-related low-grade gliomas. This should be determined by future research.

Through further experiments, the authors demonstrate that greater amounts of neuroligin-3 are released by activated neurons in the optic pathway of *Nf1*^{OPG} mice than by activated neurons in the optic pathway of regular mice. This establishes a previously unknown mechanism by which the NF1 mutation can enable neuronal activity to initiate tumours and thus make people with NF1 susceptible to them. It will be interesting to learn whether this also applies to other tumour types that are typically associated with NF1, such as malignant peripheral nerve sheath tumours. A further question would be whether other cancer-predisposition syndromes involve similar mechanisms in which neuronal activity drives tumour formation and growth.

Building again on previous work on high-grade gliomas[4,7], the authors demonstrate that a drug that inhibits the enzyme that releases neuroligin-3 from neurons does so in the optic nerves of *Nf1*^{OPG} mice, too. Treating young *Nf1*^{OPG} mice with the drug prevented optic pathway glioma formation, mimicking the effects of light deprivation. Also like light deprivation, later treatment with the drug reduced the tumour size. This compound is already in clinical trials for high-grade gliomas (see this US trial run by the Pediatric Brain Tumor Consortium; go.nature.com/3w3mx44), and so its potential for preventing or treating NF1-related gliomas is intriguing.

The study by Pan and co-workers strengthens the idea that neuronal activity not only can drive the growth of tumours, but also can be crucial for cancer initiation — which has been previously suggested to be the case in cancers outside the central nervous system[8]. In prostate cancer and other cancers, progenitor cells from the brain can even home in on tumours, where they are instrumental in tumour development and growth[9]. Furthermore, in mice, removal of neurons that carry sensory information from the pancreas to the central nervous system prevented the formation of pancreatic tumours[10]. In mouse skin, tumours were found to preferentially originate in cell populations with particularly high neuronal innervation[11]. Pan and colleagues' study extends this link to the central nervous system, and to cancer-predisposition syndromes.

So, what are the clinical implications of this study? Should we tell individuals with NF1 to wear sunglasses or cover their eyes for a certain time? Or should we somehow aim to reduce the overall neuronal activity of individuals with brain tumours? Such 'strategies' would be problematic to implement, for many practical, not to mention ethical, reasons. However, current initiatives seeking to translate our understanding of the interactions between the nervous system and cancers support the use of pharmacological approaches that are targeted to specific molecular pathways[12]. This study supports another such approach for individuals with NF1. It will be exciting to discover whether neuroscience-instructed cancer therapy will become a new pillar of treatment in oncology.

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The authors declare no competing interests.
This article was published online on 26 May 2021.

Microscopy

Squeezed light reveals molecules buried in noise

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Vibrational signals from molecules can provide contrast in bioimaging techniques, but are difficult to detect. Light in a 'squeezed' quantum state has been used to reveal molecular vibrational signals previously obscured by noise. **See p.201**

Much like fluorescence microscopy, stimulated Raman scattering (SRS) gain microscopy is an optical imaging method capable of generating high-resolution maps of biological tissues[1]. The contrast in SRS images derives from the characteristic vibrations of the sample's molecules, which enable tissue imaging without the need to label samples with fluorescent dyes. SRS is gaining ground as a biomedical imaging tool, but the minimum molecular concentrations that it can detect are higher than those that can be detected using fluorescence microscopy, thus limiting its scope. Finding ways to fundamentally improve the detection sensitivity of this technique has been challenging. On page 201, Casacio *et al.*[2] describe an approach for boosting sensitivity through quantum-enhanced suppression of noise in the SRS signal.

SRS is based on a phenomenon called the Raman effect, which involves two photons: one known as the pump photon (of frequency ω_1), which interacts with a molecule; and another called the Stokes photon (of a lower frequency, ω_2), which is radiated by the molecule in response to its interaction with the pump photon. The frequency difference ($\omega_1 - \omega_2$) corresponds to the frequency of a particular vibrational mode of the molecule. Measurements of the wavelength of the Stokes photons can therefore be used to identify the molecule on the basis of its vibrational behaviour. However, the signal produced by the Raman effect is weak, giving rise to a long integration time (the period needed to collect a signal), which prevents it from being used for tissue imaging.

SRS cleverly overcomes the weakness of the Raman signal. Unlike the linear Raman effect described above, which uses one laser beam, SRS involves illuminating the sample with two laser-light fields: a pump field with frequency ω_1 and a Stokes field with frequency ω_2. In SRS, the sample produces a stronger signal field than in the linear effect. Moreover, because the signal field is produced in phase with the Stokes field, constructive interference occurs, greatly boosting the signal from the sample (Fig. 1). The amplified signal is therefore much stronger than the weak molecular signal produced by the linear effect.

The enhanced Raman signal enables fast imaging: in some cases, SRS imaging can be up to one million times faster than that achieved