published neodymium and hafnium isotopic data, measured on archetypal kimberlites. These kimberlites cover a large age range, from less than 200 million years old up to 2 billion years old. The authors demonstrate that, over this long time period, kimberlites seem to always tap a source whose isotopic composition resembles that of the primitive mantle. This observation puts constraints on the nature of the kimberlite source, and favours a pristine reservoir — one that has survived untouched deep in the mantle for most of Earth's history.

The idea that part of the deep mantle has remained isolated from its surroundings is supported by the discovery of traces of primitive material in volcanic rocks called ocean island basalts, which might originate from regions known as seismically anomalous zones that are found at the core–mantle boundary[5,6]. A primitive source has also been attributed to many other types of rock, such as granitoids[7]. The case for a primitive kimberlite source is bolstered by the evidence that this source is deep.

For the other rock types, a near-primitive isotopic composition might be explained by the presence of recycled crust in the rock source. Woodhead *et al.* dismiss this interpretation for kimberlites by arguing that the contribution of recycled oceanic crust would have had to have been constant over the two billion years of recorded history. Moreover, they suggest that the presence of high helium ratios (ratios of helium-3 to helium-4) in diamonds of some kimberlites indicates a deep source, close to the core–mantle boundary.

The authors' interpretation might be correct, but a few independent observations need to be reconciled before the model can be applied to all kimberlites. For example, the presence of anomalous amounts of sulfur-33 in kimberlitic diamonds suggests that the source contains material that was present at Earth's surface more than 2.5 billion years ago, when the planet's atmosphere was not yet oxidized[8]. How this recycled material can coexist with the rest of the source is unclear.

Another potential concern is the unknown relationship between high helium ratios and isotopes produced by radioactive decay that are measured in diamonds. Some diamonds have low helium ratios, and strontium and lead isotopic compositions that are similar to those of Earth's crust. But no strontium and lead isotopic data are available for previously analysed diamonds that have high helium ratios[9]. As a result, such high ratios might or might not trace a pristine deep source.

Finally, kimberlitic diamonds are plucked from the mantle during ascent, and the information that they provide might be irrelevant in terms of the kimberlite source. To confirm a pristine and deep origin of kimberlites, we need to demonstrate that the kimberlite magmas themselves have pristine characteristics, such as high helium ratios, tungsten isotopic anomalies that could trace interaction of the magmas with the planet's core, and so on. A lot of work is still ahead of us. ■

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CANCER

Dangerous liaisons as tumours form synapses

Why brain tumours progress rapidly is unclear. The finding that such cancer cells form synaptic connections with neurons uncovers an interaction that accelerates tumour growth rate and lethality. SEE ARTICLES P.526, P.532 & P.539

ANDRES BARRIA

People with brain tumours have a range of symptoms that can vary in severity, from headaches to a decline in cognitive function. The symptoms depend on the tumour type and its size, location and growth rate. Understanding what controls the growth rate of brain tumours might therefore lead to the development of therapies that slow cancer progression and improve the quality of life of people who have this type of cancer. In this issue, Venkataramani *et al.*[1] (page 532), Venkatesh *et al.*[2] (page 539) and Zeng *et al.*[3] (page 526) report that, in the brain, neurons and cancer cells form a type of connection between cells called an excitatory synapse, and the formation of this connection boosts tumour growth.

An excitatory synapse is a structure in which two adjacent neurons — termed the presynaptic and postsynaptic neurons — communicate using a neurotransmitter molecule, usually glutamate (Fig. 1). Glutamate release by the presynaptic neuron activates glutamate receptors, known as AMPA receptors and NMDA receptors, on the postsynaptic neuron. Receptor activation causes ion movement across the cell membrane, which produces depolarization — an increase in positive charge inside the postsynaptic neuron that leads to excitation. Certain non-neuronal brain cells called glia surround a synapse and regulate signal transmission across it by removing released neurotransmitter[4]. Other types of glial cell affect neuronal excitability (the ease with which neurons are depolarized) by regulating extracellular potassium ions[5].

Glial cells can give rise to a type of brain tumour called a glioma, which is the leading cause of death from brain cancer in the United States[6]. One common characteristic among many different types of glioma is that their growth requires the activity of their neighbouring neuronal cells[7], but the reason has not been fully understood until now.

Healthy glial cells form interconnected cellular networks. This is because structures on the glial-cell membrane, called gap junctions, enable signalling molecules, such as calcium ions, to move into neighbouring glial cells[5]. Glioma cells also create interconnected cellular networks by forming gap junctions in what are called tumoural microtubes — long, thin, cell-membrane protrusions that extend from these cells into the surrounding tissue, and which contribute to tumour infiltration and proliferation[8].

Using an imaging method called electron microscopy, Venkataramani and colleagues examined tumoural microtubes formed by human gliomas that had been transplanted into mouse brains. They observed that the microtubes had structures characteristic of excitatory synapses, called postsynaptic densities, where glutamate receptors are normally present. Adjacent to these postsynaptic densities, in a nearby neuron, the authors noted clusters of vesicles that store neurotransmitter molecules, which are a feature of a neuronal presynaptic zone. Venkatesh and colleagues made similar observations of synaptic structures arising between glioma cells and neurons.

Venkatesh *et al.* and Venkataramani *et al.* provide evidence that genes encoding glutamate receptors and structural components of the postsynaptic region are expressed in a subset of cells in human gliomas, suggesting that glioma cells exploit the same molecular mechanisms used by neurons to establish synapses.

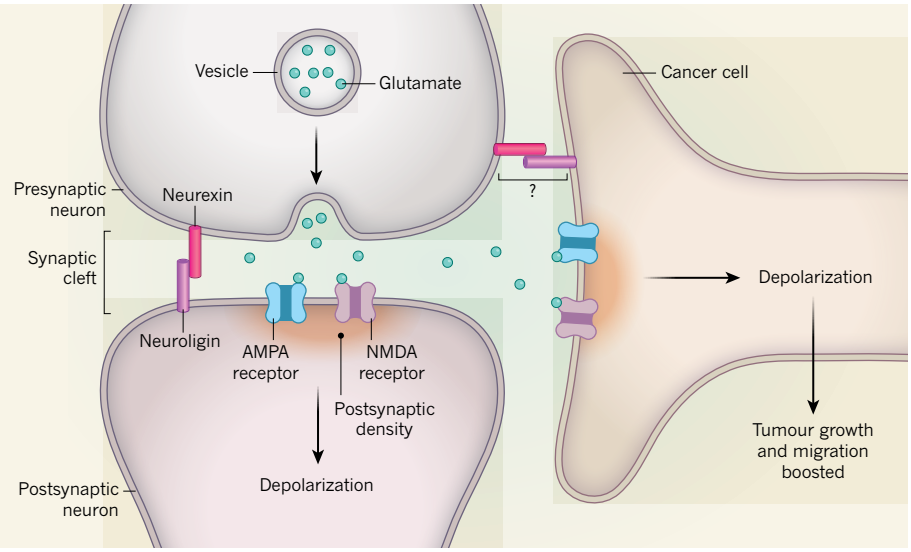

Figure 1 | Cancer cells form synaptic connections with neurons. Structures called synapses enable communication between neurons. Cell-adhesion proteins such as neurexins and neuroligins help synapses to form between neurons. In neuronal communication across a synapse, the neurotransmitter molecule (typically glutamate) is stored in vesicles and released from the presynaptic neuron. Glutamate crosses the synaptic cleft to bind and activate AMPA receptors and NMDA receptors in a structure found in the postsynaptic neuron called a postsynaptic density. Activation of these glutamate receptors causes positively charged ions (not shown) to enter the cell through the receptors, causing depolarization: a rise in intracellular positive charge. Venkataramani *et al.*[1], Venkatesh *et al.*[2] and Zeng *et al.*[3] report that human cancer cells grown *in vitro* or transplanted into mouse brains formed functional synapses with neurons. Activation of these synapses between cancer cells and neurons was associated with cancer colonization of the brain, cancer-cell migration and tumour proliferation, which helps to explain why neuronal activity is required for the growth of brain cancer. Perhaps neuroligin aids synapse formation between cancer cells and neurons. Where it might act, and whether it binds neurexin, in such synapses is unknown.

To determine whether synapses between tumour cells and neurons function in a similar way to those formed between neurons, both groups transplanted human glioma cells into mouse brains. The stimulation of neurons near the glioma cells produced a rapid depolarizing current in some glioma cells characteristic of excitatory synapses, and this current was mediated by AMPA receptors. Crucially, the type of AMPA receptor expressed in these glioma cells has different pharmacological properties from the AMPA receptors expressed in neuron, making it a promising candidate as a drug target. In some of the other glioma cells, a long-lasting depolarizing current was observed that amplified and spread through gap junctions to the connected network of tumour cells. This prolonged current was not of a synaptic origin — instead, it seemed to come from changes in the extracellular concentration of potassium ions as a result of neuronal activity.

The depolarization of glioma cells induced by neuronal activity caused a transient rise of calcium ions in the cytoplasm, which then spread through the network of glioma cells through their gap junctions. A higher frequency of these calcium signals correlated with increased migration of some of the tumour cells in the network, indicating that synapse formation in a tumour cell altered the properties of other cells in the tumoural network and increased their invasiveness.

To determine the biological importance of the synapses formed between glioma cells and neurons in their model systems, Venkatesh *et al.* and Venkataramani *et al.* used either pharmacological tools or genetically engineered glioma cells to block AMPA receptors and thereby prevent depolarizations induced by synaptic activity. These treatments led to an increase in the survival time of animals that had received a transplant of human glioma cells, compared with control animals in which AMPA receptors were not blocked. These manipulations of AMPA receptor function therefore caused a substantial reduction in the effect of synaptic stimulation on the proliferation and invasiveness of glioma cells.

Both groups also engineered human glioma cells to express a light-activatable version of an ion channel that produces cellular depolarization, similar to that obtained by the synaptic-mediated activation of glutamate receptors. Such cells were transplanted into the brains of mice by Venkatesh *et al.* or grown *in vitro* by Venkataramani and colleagues. When light was used to depolarize the glioma cells, this promoted tumour proliferation.

Together, the evidence from Venkatesh *et al.* and Venkataramani *et al.* indicates that some glioma cells have the capacity to form functional synapses with neurons that are present in their microenvironment. Moreover, these cells form an electrically active tissue that can signal to other glioma cells in the tumour-cell network to promote their migration and growth. The presence of functional synapses between neurons and cancer cells explains why glutamate-mediated neurotransmission is associated with enhanced proliferation, survival and invasiveness of glioma cells[9–12].

Zeng and colleagues investigated the role of glutamate-mediated signalling in tumours by examining the expression of glutamate receptors in many different sorts of human cancer. Breast cancer cells, a type of tumour cell that often migrates to the brain, had higher expression of NMDA receptors compared with other types of tumour that they studied. A protein subunit of NMDA receptors called GluN2B — required for synapse formation[13] and for changes in the strength of synaptic connections[14] — was highly expressed in human and mouse breast cancer cells that the authors determined have a high capacity to migrate to the brain. NMDA receptors allow calcium ions to enter cells and have been implicated in aiding the progression of some human cancers[15]. Using techniques that included an imaging approach to track calcium levels and electrophysiological recordings, Zeng and colleagues report that NMDA-receptor-mediated signalling occurred in mouse breast cancer cells.

Human breast cancer cells express neuroligin, a protein that aids adhesion between cells and that normally contributes to the formation of synaptic structures between neurons. This suggests that, in a similar way to human glioma cells, human breast cancer cells might exploit the standard mechanisms used by neurons to establish synaptic connections. Indeed, when Zeng *et al.* used microscopy techniques to study samples of mouse tissue containing human breast cancer cells that had been injected into the animals' brains, they observed that proteins involved in packing glutamate into vesicles were in close proximity to NMDA receptors, and that synaptic structures had formed between the cancer cells and the neurons. Finger-like cellular processes extended from the cancer cells to reach existing mouse synapses between neurons, adopting the same typical position around a synapse as is adopted by glial cells that remove glutamate from the synaptic cleft. Such an arrangement would allow cancer cells to obtain glutamate to activate their NMDA receptors.

Zeng and colleagues report that, if mice received breast cancer cells engineered to have reduced GluN2B expression, the cells produced smaller brain tumours and the animals had a longer survival time compared with animals that received breast cancer cells with normal GluN2B levels. These results indicate that the signalling mediated by the NMDA receptor promotes the colonization and growth of cancer cells in the brain.

Together, these three studies demonstrate that brain tumours can establish synaptic connections with neurons using the molecular toolkit that forms synapses between neurons. In neurons, synaptic activity enables the

depolarization and calcium-ion influx that is necessary for cellular differentiation, proliferation and survival. In cancer cells, these same processes instead support the proliferation of the tumour and contribute to cancer's eventual lethality. These intriguing findings raise the possibility that approaches targeting specific types of glutamate receptor, postsynaptic signalling processes or the mechanisms needed for synapse formation might provide therapeutic targets for slowing tumour proliferation. ■

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ECOLOGY

Captivity concerns for monarch butterflies

Monarch butterflies' ability to migrate over long distances is impressive. Evidence that some monarchs reared in captivity have impaired migratory skills compared with wild monarchs has conservation implications.

KAREN S. OBERHAUSER

The eastern population of North American monarch butterflies (*Danaus plexippus*) migrates annually in early autumn to a mountainous region in central Mexico. The incredibly long distances covered during these journeys, and the striking sight of these butterfly populations on the move have captivated people's imaginations. Writing in the *Proceedings of the National Academy of Sciences*, Tenger-Trolander *et al.*[1] document the loss of migratory behaviour in monarchs that had been bred in captivity over multiple generations.

Tenger-Trolander and colleagues' research has captured the attention of a broad community of individuals, including scientists, conservationists, people who breed butterflies for commercial purposes, the media and monarch-butterfly aficionados. Commercial breeders of monarch butterflies produce large numbers of butterflies that are sold for educational purposes or for mass-release events at special occasions such as weddings, for example. 'Citizen scientists' and educators often raise, in comparatively small numbers, monarchs that they have collected from the wild as eggs or larvae, and which they release when the adult butterflies emerge from the pupae.

Monarch numbers have declined in recent decades[2,3], leading to a petition for them to be listed as threatened species under the Endangered Species Act in the United States (see go.nature.com/2ipcsc2). The solutions needed to tackle this decline are not straightforward. Many researchers and conservation groups have expressed worries about efforts focused on the release of captively reared monarchs, citing concerns that such releases might have negative consequences for the genetic diversity of butterfly populations and might introduce disease (see go.nature.com/2iw8rhk).

The first key conclusion of Tenger-Trolander and colleagues' work is that commercially bred monarchs can be highly different genetically from individuals from wild populations, and that these differences can result in the loss of the butterflies' propensity to migrate. The authors studied migratory behaviour using a flight simulator (Fig. 1a) that allowed them to compare the flight paths of wild North American monarchs to those of the offspring of commercially bred individuals.

When both the wild and commercially obtained groups were reared outside and emerged in mid-August, they did not exhibit strong directional flight, and the females produced eggs. This is to be expected; in the summer, monarchs focus on finding mates, nectar-bearing plants and their milkweed host plants for egg-laying, rather than migrating. However, in the autumn, eastern North American monarchs migrate south, and are in reproductive diapause, a hormonally driven condition that is characterized by the lack of maturation of reproductive organs[4], and which is triggered by changes in day length and temperature conditions experienced during development[5]. When Tenger-Trolander and colleagues reared monarchs outside during the time that wild migratory monarchs would

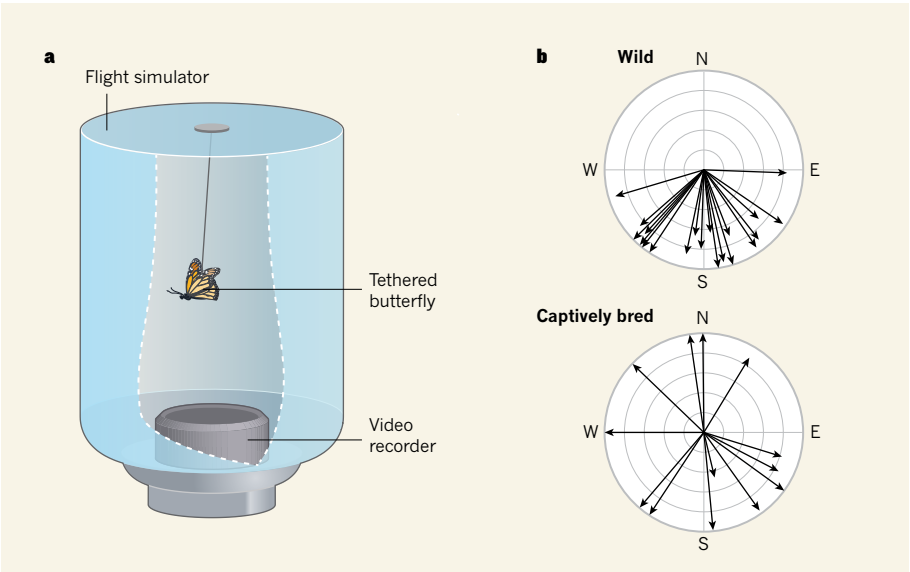

Figure 1 | The flight path of monarch butterflies. **a**, Tenger-Trolander *et al.*[1] studied monarchs (*Danaus plexippus*) using a flight simulator. In this apparatus, the direction of flight of tethered butterflies is tracked using a video recording device at the base of the simulator. **b**, When the authors studied wild monarchs reared outside that emerged in the autumn, at a time when wild monarchs normally migrate south, these butterflies flew in a southerly direction, as expected. In the flight-simulator data shown, each line represents the mean flight direction for each butterfly, and longer lines represent a stronger preference. Captively bred monarchs that were reared outside and that emerged in the autumn did not show any specific directional preference in their flight path.