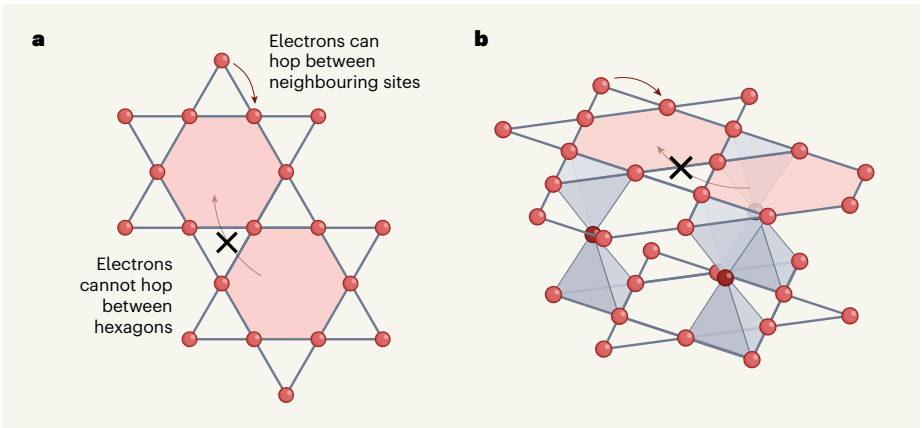

Figure 1 | Crystal lattices hosting flat bands. Electrons occupy orbitals with discrete energy levels, but, in solids, they can hop between atoms, causing these energy levels to form bands. If the bands are flat, the energies of the electrons do not change with their momenta, and this can lead to unusual physical phenomena. **a**, The 2D kagome lattice comprises corner-sharing triangles and hosts flat bands because electrons can hop between neighbouring sites, but are localized in each hexagon and cannot move from one hexagon to the next. **b**, Wakefield *et al.*[3] showed that flat bands also arise in a 3D solid containing a structure known as a pyrochlore lattice, raising hopes of finding more 3D flat-band materials.

and nickel ($CaNi_2$) as the right material for the job, because the nickel in this metal forms a pyrochlore lattice, as required by theory. They then used ARPES to probe the 3D electronic structure of $CaNi_2$, and observed flat bands extending along all three directions of the crystal lattice. These bands are not as flat as theory would suggest, partly because they mix with other bands, and also as a result of complications arising from the calcium atoms in $CaNi_2$. However, the authors' results represent a huge step forward in the effort to find 3D flat-band materials.

Flat bands produce exotic behaviours only when they lie close to the Fermi level, which is the highest energy level that is occupied by electrons. Wakefield and colleagues showed that the energy position of the flat bands can be tuned, by adjusting the chemical composition of another material with a pyrochlore lattice, $Ca(Rh_{1-x}Ru_x)_2$, which contains rhodium (Rh) and ruthenium (Ru) along with calcium. They were able to engineer the $Ca(Rh_{1-x}Ru_x)_2$ so that the flat band was very close to the Fermi level, and this enhanced the correlations between electrons, leading to the appearance of superconductivity with a relatively high critical temperature of 6.2 kelvin.

The effect of a flat band is expected to be more pronounced in 3D materials than it is in 2D materials. Flat bands combine strong electron correlations with topological behaviour, both of which are conducive to the formation of unusual phases. And certain phenomena and states of matter can be realized only in flat-band systems that have high dimensions[16,17].

Wakefield and colleagues' discovery of 3D flat bands has therefore created a new platform for studying these intriguing behaviours. It opens a path for finding other materials with 3D flat bands, and for investigating the exotic states that they are expected to host. The authors' demonstration that such bands can be engineered with chemical (and perhaps mechanical) tuning will have an important role in all these endeavours.

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Tumour biology

Cancer hijacks neuronal learning mechanisms

Matthew B. Dalva

Synaptic connections between cancer cells and neurons can boost tumour growth. Analyses of brain tumours reveal how cancer cells enhance the strength of synapses with neurons to promote tumour survival. **See p.366**

Cancer often results from the dysregulation of normal cellular mechanisms, because tumour cells can co-opt such processes to increase their own survival, proliferation and invasiveness. A great deal of effort has been made to develop therapies that target these processes, with the goal of slowing the growth of the tumour cells, reducing their proliferation or killing them. However, many cancers — particularly those of the brain — have not been successfully targeted by this approach, which suggests that other factors are involved in mediating cancer progression. On page 366, Taylor *et al.*[1] reveal that brain cancer harnesses an unexpected type of cellular process.

One mechanism that seems to increase the survival and invasiveness of tumour cells is their communication with the surrounding cellular environment[2,3]. These interactions have a central role in determining cancer progression and prognosis, and could therefore be a powerful therapeutic target. Taylor and colleagues show that brain tumours called gliomas and glioblastomas can hijack mechanisms that are normally associated with neuronal connections called synapses (Fig. 1).

The tumours take advantage of a process known as the adaptive neuronal plasticity of synapses, in which the strength of the connections between neurons can be increased or decreased in response to stimuli. These changes in synaptic strength often occur at excitatory synapses, at which the neurotransmitter glutamate is released. Adaptive increases in synaptic strength are thought to mediate the encoding, storage and retrieval of information, thus forming the basis of memories and learned behaviours. By targeting the

plasticity mechanisms that are hijacked by brain cancers, Taylor *et al.* were able to slow tumour growth and improve survival in animal models of types of glioma and glioblastoma that have resisted many other therapeutic strategies.

Gliomas and glioblastomas (see go.nature.com/42ty15h) are tumours that originate from non-neuronal cells in the central nervous system called glial cells, which are crucial regulators of brain and synaptic function. These types of brain cancer have a poor clinical prognosis. Paediatric glioblastomas, in particular, are a rare but aggressive form of brain tumour[4] with a median survival time of 12–15 months and 5-year survival rates of less than 20% – outcomes much worse than those for most paediatric brain tumours[5]. The neurons that surround gliomas and glioblastomas form excitatory synapses with tumour cells.

Unlike adult glioblastomas, most paediatric glioblastomas express high levels of an enzyme in the brain called TRKB that functions as a receptor (ref. 6). TRK receptors (TRKB and another enzyme, TRKC) are activated by a protein called BDNF, and this signalling between TRK receptors and BDNF regulates neuronal growth, survival and plasticity. In the process of neuronal plasticity, the activation of TRKB by BDNF increases synaptic strength by triggering the recruitment of a receptor for glutamate, AMPAR, to the cell surface at synapses[7].

The molecular and cellular mechanisms that underlie synaptic plasticity were the focus of intense investigation from the 1980s to the 2000s, and this work resulted in a detailed understanding of how change at the neuronal synapse is mediated[8]. Technologies and techniques were developed to visualize and modulate changes in synaptic strength, and the molecular pathways responsible were elucidated. However, whether these insights could have therapeutic utility has remained unclear. Taylor *et al.* now build on this body of research to uncover the ways in which brain tumours hijack plasticity mechanisms at synapses to promote their own growth and survival.

Synaptic AMPARs mediate the entry of positive ions across the cell membrane, a process termed depolarization. The synaptic connections between neurons and glioma cells use a type of AMPAR that can enable calcium to enter the cell. Such receptors are found at some normal synapses between neurons, and they can induce plasticity. The presence of calcium-permeable AMPARs at glioma–neuron synapses can enable activity-dependent changes. Notably, Taylor and colleagues find that one of the previously described[7] mechanisms of neuronal plasticity – TRKB-dependent increases in the localization of AMPAR to synapses, which strengthens synaptic connections and boosts neuronal activity – seems to be a potent regulator of glioma-cell vigour.

Many mechanisms can increase synaptic plasticity, including rapid influxes of calcium in the region of the synapse known as the postsynaptic terminal (the side of the synapse that receives neurotransmitters), and postsynaptic activation of TRKB. The high levels of TRKB that are observed in paediatric gliomas and glioblastomas, together with the presence of synapses between neurons and cancer cells, suggested to Taylor and colleagues that TRKB signalling might have a role at these abnormal synapses in tumours. To test this theory, and establish whether disrupting BDNF–TRKB signalling might have therapeutic potential, the authors used several model systems, together with drugs that inhibit the function of TRK enzymes.

Taylor *et al.* applied a technique called optogenetics to artificially stimulate neurons in the brains of mice that had been transplanted with human glioma cells, and found that this significantly increased tumour growth rates and reduced survival times. However, when the authors used a *Bdnf*-mutant mouse model, in which the activity-induced expression of BDNF is diminished, they found that the effects of neuronal stimulation on tumour progression were markedly reduced. BDNF thus enhances the proliferation of glioma in mice transplanted with human cells and in cells grown *in vitro* from people with cancer grown *in vitro*. Genetic engineering to remove the gene that encodes human TRKB in cells from people with glioma slowed tumour progression and increased the survival rate of mice that were transplanted with these cells, compared with mice that were transplanted with human cells expressing the wild-type version of the gene. Treatment with pan-TRK inhibitors enhanced the survival of mice transplanted with human glioma cells, but this effect was not observed in mice with the engineered glioma cells lacking TRKB. These data indicate that TRKB signalling can regulate the progression of glioma tumours.

Gliomas contain several subpopulations of cells, which are named on the basis of their similarity to normal cell types in the nervous system. These include astrocyte-like cells, which are similar to astrocytes (glial cells that support neuronal function); oligodendrocyte-like tumour cells, which resemble oligodendrocytes (cells that wrap around the axonal projections of neurons); and oligodendrocyte-precursor-like cells. Using single-cell RNA-sequencing data from human tumours, the authors examined the relationship between TRKB expression and the glioma cell types. In the astrocyte-like cells, expression of TRKB was associated with that of proteins related to microtubules, which are components of part of the cellular architecture called the cytoskeleton. By contrast, in oligodendrocyte-like or oligodendrocyte-precursor-like cells, TRKB expression was linked with that of synaptic genes, particularly those related to pre- and postsynaptic function.

Taylor *et al.* report that neuronal activity not

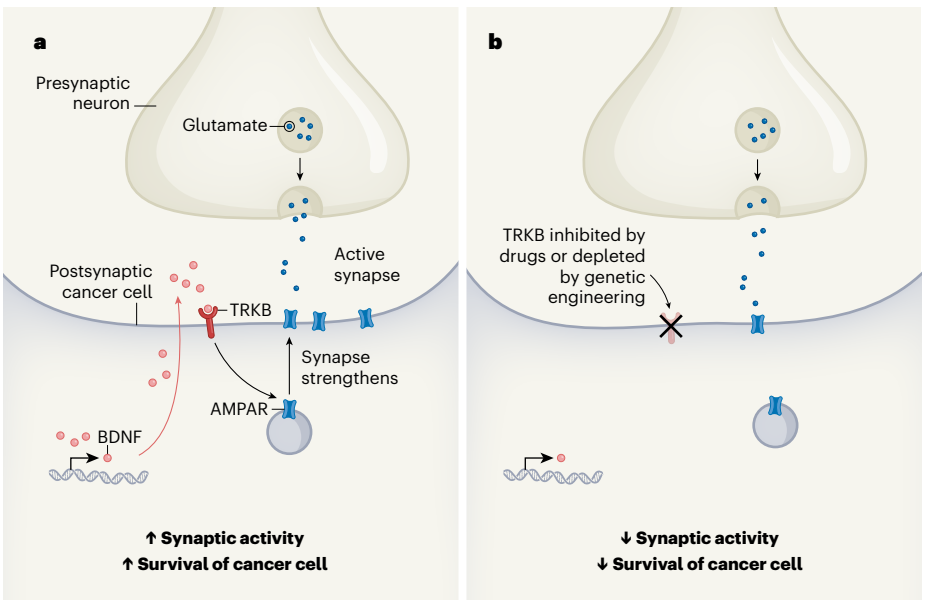

Figure 1 | Connections between brain-cancer cells and neurons. a, Taylor *et al.*[1] examined the strength of connections (also known as synaptic plasticity) found at structures termed synapses. Synapses form between neurons and cancer cells that are described as presynaptic and postsynaptic cells, respectively. These neurons release the molecule glutamate, and activity at these synapses drives the expression of the protein BDNF, which binds to the receptor protein TRKB. Signalling through TRKB increases the number of receptors of the glutamate-binding protein AMPAR that reach the surface of brain-cancer cells. Ions (not shown) flowing through AMPAR boost the activity of the synapse. **b**, The authors report that blocking TRKB activity, depleting TRKB or blocking activity-dependent BDNF expression inhibits signalling through the receptor, reducing TRKB-dependent synaptic plasticity in the synapse and reducing cancer-cell survival.

only directly stimulates the growth of gliomas, but also reinforces the interactions between neurons and glioma cells. Building on previous work[9], the authors find that the expression of certain genes related to synaptic interactions (for example, genes that encode synaptic adhesion factors) might boost the formation of synaptic contacts, whereas BDNF–TRKB signalling acts to enhance synaptic strength through mechanisms linked to synaptic plasticity. Many different types of cancer generate synapse-like contacts with the surrounding tissue, which suggests that the mechanisms described by Taylor *et al.* might be of broader relevance for understanding tumour progression.

Consistent with well-established mechanisms in the brain[7,8,10], Taylor and colleagues found that treating transplanted glioma cells with BDNF promoted the trafficking of AMPAR to the cell membrane (Fig. 1). The effects of BDNF on gene expression in paediatric tumour cells were modest, which suggests that the primary role of BDNF in these cells is at the level of the protein rather than the gene. To determine whether the BDNF-dependent regulation of AMPAR and glioma–neuron synapses uses the same mechanisms as those underlying neuronal plasticity, the authors took a variety of approaches (electrophysiology, electron microscopy, immunostaining and optogenetics). These data show that post-synaptic modulation of glioma synapses uses similar mechanisms to those[8,10] that mediate adaptive synaptic plasticity.

Targeting this maladaptive plasticity might offer a new way to treat gliomas. Taylor *et al.* suggest that pan-TRK inhibitors such as entrectinib or larotrectinib – which are already approved for treating other malignancies – could also be used to reduce the survival and invasiveness of paediatric gliomas by targeting TRKB-dependent synaptic plasticity.

In the nervous system, neuronal activity and neuronal growth factors are key determinants of survival; however, increases in the activity of neurons can accelerate tumour progression. Taylor *et al.* show that the survival and malignancy of tumour cells are boosted by the ability of these cells to hijack neural mechanisms that increase synaptic strength, and possibly synaptic number.

These data are part of a growing body of evidence suggesting that synaptic dysfunction has a central role in many brain diseases. Thus, conditions as diverse as neuropathic pain, schizophrenia, autism spectrum disorders, motor neuron disease (amyotrophic lateral sclerosis), Alzheimer's disease and now cancer are linked to dysfunction of the synapse[11–13]. Future work could investigate whether diseases associated with synaptic dysfunction (synaptopathy), such as brain cancer, can be treated by blocking synaptic plasticity. This strategy might have less detrimental consequences for brain function than do broad-spectrum therapeutic approaches, and might have a more targeted effect on tumour progression.

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