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Tumour biology

Neurons aid growth of small-cell lung cancer

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Signalling between neurons and tumour cells in the lung and brain promotes the growth of small-cell lung cancer. These interactions might be a therapeutic target. **See p.1232 & p.1243**

Some cancers benefit from interacting with the nervous system – either by directly forming functional connections, termed synapses, with neuronal cells or by indirectly receiving signals released from neurons. This phenomenon is most commonly studied in brain cancers, such as gliomas, but tumours located elsewhere can also benefit from interactions with neurons[1,2]. Writing in *Nature*, Savchuk *et al.*[3] (page 1232) and Sakthivelu *et al.*[4] (page 1243) reveal that neuron–cancer interactions promote the growth of small-cell lung cancer (SCLC) – a highly aggressive type of lung tumour that often spreads to the brain, and has only limited treatment options[5].

Conventionally, SCLC has been thought to arise from pulmonary neuroendocrine cells (PNECs), a rare type of cell that can form connections with sensory and motor neurons arising from the vagus nerve (a key component of the branch of the nervous system that regulates breathing, heart rate and digestion). Given that SCLC cells have many characteristics in common with PNECs, it is feasible that SCLC could similarly form connections with neurons, enabling them to promote tumour initiation, growth or spread. Indeed, SCLC cells can have electrical activity (a hallmark of neurons), which promotes malignancy[6].

SCLC cells with higher expression of genes associated with neuronal signalling and communication using neurotransmitter molecules have an increased risk of cancer spread (metastasis) and are associated with poor survival rates[6,7]. Savchuk and Sakthivelu and their respective colleagues used mouse models and human cell lines to explore whether and how SCLC interacts with neurons in the lung and in the brain, with the goal of uncovering targets that might lead to the development of effective treatment strategies.

Both studies provide compelling evidence that signalling between neurons and cancer cells promotes SCLC growth. Sakthivelu *et al.* examined more than 300 lung tumours from genetically engineered mouse models of SCLC. They used an innovative gene-editing approach called *piggyBac* insertional mutagenesis, which enabled them to identify mutated versions of genes that promote tumour growth or survival. These included genes involved in synapse formation and neuronal signalling, several of which were found to be mutated in a subset of 456 human SCLC samples. Both studies also observed neurons growing intertwined with SCLC tumour cells in mouse models and human tumours – prompting the authors to investigate this innervation and the functional interactions between SCLC cells and the nervous system.

"Tumour cells near neurons displayed increased proliferation compared with those farther away."

Using a variety of complementary techniques – such as growing neurons and tumour cells taken from mice and humans together in a dish, mouse models, microscopy and methods to manipulate neuronal activity (optogenetic approaches) – the authors examined how neuron–cancer interactions promote SCLC growth. Growing SCLC cells in a dish with neurons increased tumour-cell proliferation compared with growth of the cells without neurons. The ability of neurons to promote SCLC proliferation was prevented by treatment with the molecule tetrodotoxin, which blocks neurons from generating an electrical signal called an action potential.

Savchuk *et al.* show that growing neurons with SCLC cells resulted in changes in gene expression at the single-cell level for SCLC cells, compared with culturing them without neurons. Growing the two cell types together drove a rise in the expression of genes associated with synapse formation and the production of receptors for neurotransmitter molecules in SCLC cells. Neuronal activity increased SCLC growth and altered SCLC characteristics. Notably, this growth-promoting effect was specific to SCLC, because when another type of lung cancer – non-small cell lung cancer – was grown with neurons, there was only a minor increase in proliferation of the cancer cells under the same conditions.

Using an *in vivo* approach, Savchuk and colleagues investigated whether inhibiting the forging of connections from neurons to SCLC reduces tumour formation and growth. Using a SCLC mouse model with neuroendocrine-high tumours (those with similarities to neuroendocrine cells), the authors surgically cut one branch of the vagus nerve to block neuronal input to the lung. This slowed or prevented SCLC initiation, reduced tumour growth and prolonged survival times. However, when this surgery was performed after tumours had formed, there was no effect on tumour growth or survival times, suggesting that neuronal input is important for tumour initiation rather than progression.

In contrast to the neuroendocrine-high mouse model, interfering with the neurons had no effect in a mouse model[8] of a more-aggressive type of SCLC with tumours that have high expression of the gene *Myc* and fewer neuroendocrine characteristics – which represent around 20% of human SCLC tumours[9]. Therefore, the influence of neurons on SCLC in the lung is probably context dependent.

Savchuk and colleagues explored how interactions between neurons and cancer cells drive tumour growth in the brain. Similarly to their findings from lung studies, the authors report that SCLC-derived brain tumours were infiltrated by neurons, and that tumour cells near neurons displayed increased proliferation compared with those farther away. Savchuk *et al.* found that stimulating neuronal signalling using sophisticated optogenetic techniques was sufficient to increase SCLC cell proliferation and local tumour spread in the brain. Thus, SCLC interactions with neurons can promote tumour growth in the lung and brain, and potentially tumour spread in the brain (Fig. 1).

Neurons might influence the growth of SCLC tumour cells through direct or indirect interactions. Both studies present evidence, gathered using high-resolution microscopy

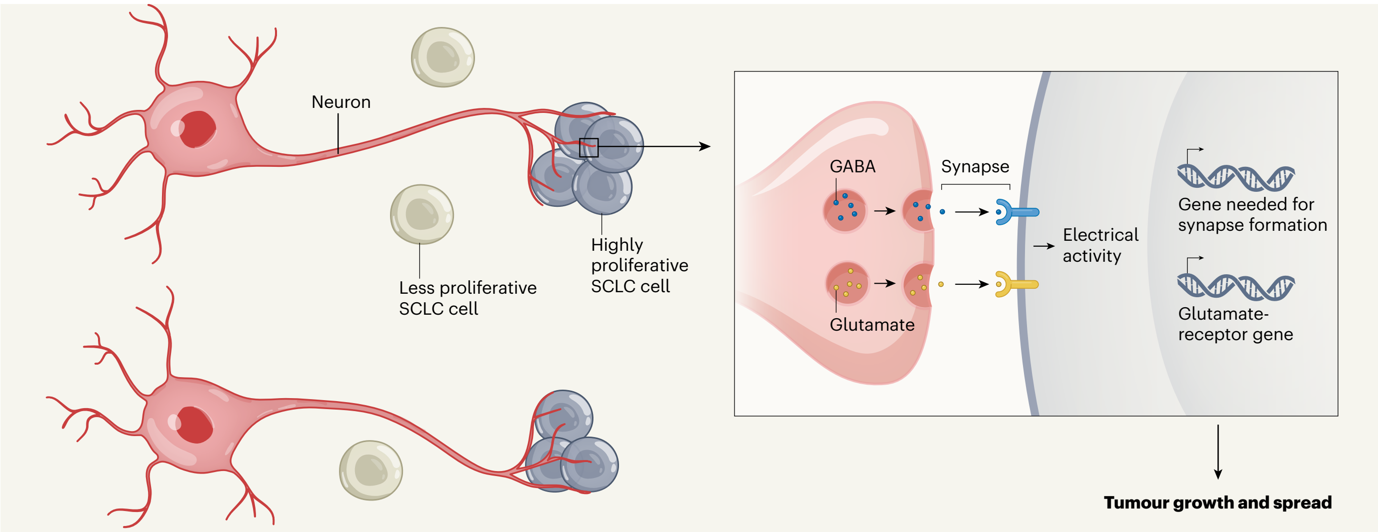

Figure 1 | Interactions between neurons and lung cancer cells that aid tumour growth. Savchuk *et al.*[3] and Sakthivelu *et al.*[4] studied a hard-to-treat type of lung cancer called small-cell lung cancer (SCLC) using mouse models and human cells. At its primary site of growth in the lung or when it has spread to the brain, the cancer is found growing alongside nerves. SCLC cells near nerve endings divide more frequently than do SCLC cells that are farther away. Neurons can interact with SCLC cells through a type of connection called a synapse. The neuron releases the molecules GABA and glutamate, which bind to their respective receptors on the SCLC cell. This drives electrical activity in the SCLC cell and leads to tumour growth and spread. Signalling between the neuron and the SCLC cell drives a rise in the expression of genes needed for synapse formation and of genes encoding glutamate receptors.

techniques, for the presence of functioning synapses between SCLC and neurons. The authors demonstrated that these synapses were functional using the method of whole-cell electrophysiological recordings on thin slices of tissue from a brain region called the hippocampus, which contained SCLC cells.

The recordings provided signs of working synaptic connections, capturing a feature called excitatory post-synaptic currents in SCLC cells. These currents could be prevented by treatment of brain slices with various inhibitors that target distinct aspects of synaptic signalling, such as transmission of the neurotransmitter molecule glutamate. Placing SCLC cells in the nutrient-media solution taken from neurons grown in a dish led to only minor increases in SCLC proliferation, suggesting a more dominant role for direct-contact-mediated signalling than for signalling induced by released molecules.

To explore the potential clinical relevance of these findings, Savchuk *et al.* treated mice with a drug that impedes the release of vesicles from synapses to prevent post-synaptic current activity in SCLC cells. This treatment reduced SCLC growth in the brain.

Sakthivelu and colleagues treated SCLC-bearing mice with an inhibitor of glutamate release alone or in combination with standard-of-care chemotherapy. Both the inhibitor and the inhibitor combined with chemotherapy reduced tumour growth and prolonged survival compared with controls (no treatment) or chemotherapy alone. However, treatment with an inhibitor of the GRM8 glutamate receptor present in SCLC was not effective when combined with chemotherapy. Targeting neurotransmission might be a promising therapeutic avenue for SCLC treatment, but future efforts will be needed to identify and test more-specific drugs and find the contexts, such as genetic backgrounds, in which they might be effective.

SCLC has four distinct molecular subtypes categorized by the expression of specific transcription factors[5]. Each subtype might respond differently to certain therapies[5], and there is a growing appreciation that SCLC subtypes might differ in how they interact with neighbouring non-tumour cells. Therefore, a key question is whether the growth of particular SCLC subtypes are more reliant than others on neuronal interactions. Both studies report that neuronal interactions promote SCLC growth in an apparently subtype-independent manner in human cells. However, a previous study[6] showed that only certain subtypes of SCLC cell have electrical activity. Savchuk *et al.* note that tumours in MYC-driven SCLC mouse models were not inhibited by neuronal removal. Thus, whether the effect of neuronal interactions and related therapies might be limited to some subtypes of SCLC warrants further investigation, in models including newly developed ones that better mirror the subtype diversity of the human disease[10].

SCLC models that are derived from lung basal cells more faithfully give rise to SCLC tumours with multiple subtypes (similar to human tumours), challenging the view that PNECs are the primary cell of origin of SCLC[10]. Unlike PNECs, lung basal cells are not connected to neurons, but might still respond to neuronal molecular signals. Therefore, determining whether neuronal connections drive tumour growth in basal-cell-derived models and whether these interactions can be targeted is a future direction of research to pursue.

Could neurotransmitter inhibition block SCLC spread to the brain? Although Savchuk and Sakthivelu and their respective colleagues show the effectiveness of blockade of neuronal signalling in models in which tumours are transplanted into mouse brains, thorough investigation is currently hampered by a lack of adequate models for studying SCLC spread to the brain. Developing these will be an essential step for determining whether targeting neuronal signalling is a viable intervention strategy to stop SCLC from reaching the brain.

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