Nature Reviews Drug Discovery | Published online 30 Oct 2017; doi:10.1038/nrd.2017.216

ANTICANCER THERAPY

Holding the thought

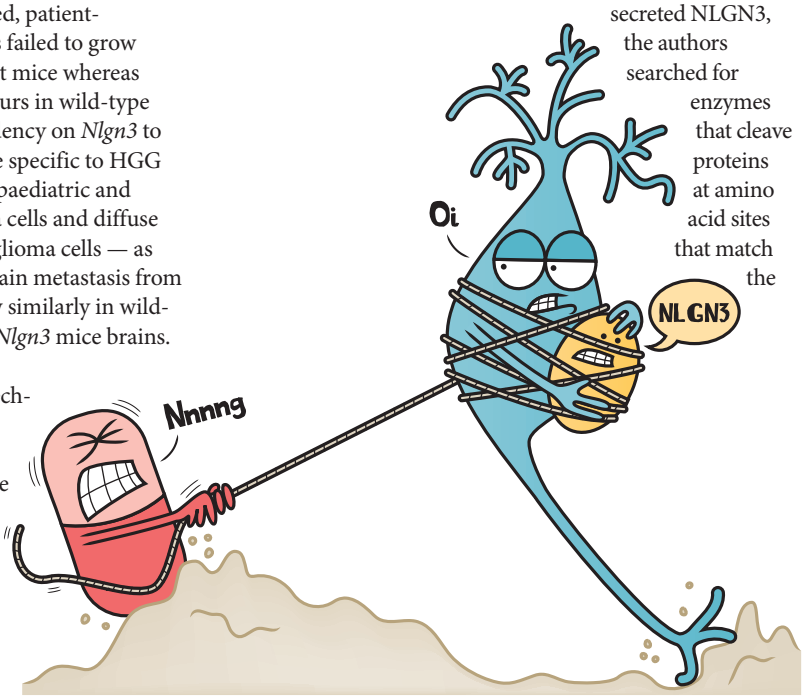
High-grade gliomas (HGGs) are the most lethal type of brain tumour in both children and adults. The heterogeneous nature of these tumours and the lack of targetable mutations have hampered the development of effective therapies. Now, a group, led by Michelle Monje, has described how inhibition of the cleavage and secretion of the synaptic adhesion molecule neuroligin 3 (NLGN3) by normal neurons in the microenvironment impairs glioma growth, offering a new approach to treat these tumours.

The role of the microenvironment in promoting the growth of HGGs is becoming increasingly clear. Previously, the authors had shown that NLGN3 secreted by neurons adjacent to the tumour can promote tumour proliferation through activation of the PI3K–mTOR pathway in glioma cells. Indeed, patient-derived HGG cells failed to grow in *Nlgn3*-knockout mice whereas they formed tumours in wild-type mice. This dependency on *Nlgn3* to grow seemed to be specific to HGG cells — including paediatric and adult glioblastoma cells and diffuse intrinsic pontine glioma cells — as patient-derived brain metastasis from breast cancer grew similarly in wild-type or knockout *Nlgn3* mice brains.

> “Inhibition of the cleavage and secretion of … [NLGN3] by normal neurons in the microenvironment impairs glioma growth, offering a new approach to treat these tumours”

To gain further insight into the mechanism by which NLGN3 drives tumour growth, the authors carried out a phosphoproteomic analysis at different time points after glioma cells were exposed to NLGN3 and observed phosphorylation of focal adhesion kinase (FAK), which resulted in the activation of downstream signalling targets including SRC, PI3K, mTOR and mitogen-activated protein kinase (MAPK). FAK inhibition blocked the effects of NLGN3 on glioma proliferation.

How is NLGN3 secreted? Can that be inhibited too? Full-length NLGN3 is expressed on the surface of neurons and oligodendrocyte precursor cells (OPCs), and further experiments revealed that both cell types are a source of secreted NLGN3. Interestingly, NLGN3 exposure results in feedforward expression of NLGN3 in glioma cells, which also contributes to the pool of NLGN3 found in the tumour microenvironment. To find the enzyme responsible for cleaving full-length NLGN3 into extracellular secreted NLGN3, the authors searched for enzymes that cleave proteins at amino acid sites that match the cleavage pattern observed in extracellular NLGN3. Through a combination of pharmacological and genetic mouse modelling experiments, they identified disintegrin and metalloproteinase domain-containing protein 10 (ADAM10). As expected, pharmacological inhibition of ADAM10 did not inhibit proliferation of adult or paediatric HGG cells *in vitro* in the absence of the microenvironment. However, administration of the ADAM10 inhibitor, GI254023X, and the ADAM17/10 inhibitor INCB7839, to mice bearing tumour xenografts derived from paediatric glioblastomas and diffuse intrinsic pontine gliomas inhibited the growth and progression of these tumours.



Macmillan Publishers Limited/Neil Smith

Inhibitors of the human ADAM family of enzymes, such as INCB7839, have been developed and assessed in clinical trials for the treatment of other cancers, such as lymphoma and breast cancer, and therefore these inhibitors could potentially be repurposed to treat patients with HGG. According to Monje, ADAM10 inhibition seems more promising than FAK inhibition as NLGN3 must have multiple effects in glioma and blocking its release into the microenvironment is probably more effective than blocking only one of the multiple signalling pathways that are likely involved. However, as the authors note, ADAM10 mediates the cleavage of many other proteins, including the amyloid-β protein, and therefore the long-term effects on neurological function should be carefully evaluated.

M. Teresa Villanueva

ORIGINAL ARTICLE Venkatesh, S. H. *et al.* Targeting neuronal activity-regulated neuroligin-3 dependency in high-grade glioma. *Nature* **549**, 533–537 (2017)