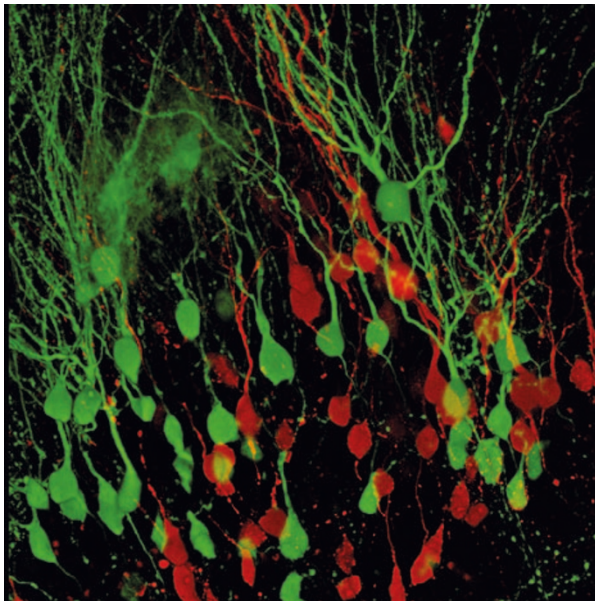
NEUROGENESIS

Does age matter?



Confocal image of mature dentate granule neurons born during development (green) and adulthood (red). Dividing progenitor cells of the developing and adult dentate gyrus of the same mouse were labelled by retroviral transduction with green (GFP) or red fluorescent proteins (mRFP1), respectively. Image courtesy of V. C. Piatti and N. A. Morgenstern, Fundación Instituto Leloir, Buenos Aires, Argentina.

New neurons are generated in the hippocampal dentate gyrus throughout life. Although immature neurons born in adulthood differ in their functional properties from neurons born perinatally, it is unknown whether this distinction continues to exist upon maturation of the cells. Two recent studies set out to answer this question, finding both similarities and differences between old and young mature neurons.

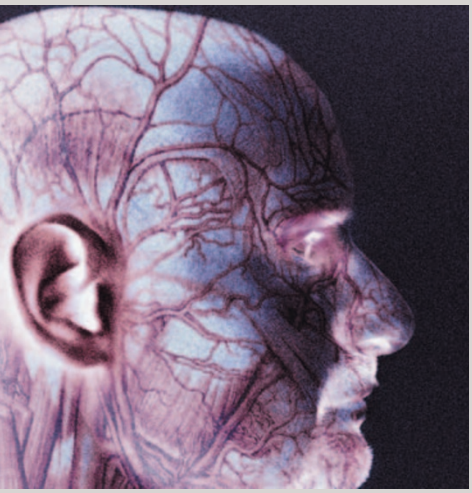
In a series of experiments in mice, Laplagne *et al.* used double retroviral labelling so that neural progenitor cells born perinatally were labelled with a green fluorescent marker, whereas cells born in adulthood were labelled red. When the mice were 19 weeks old and all labelled neurons had matured, electrophysiological recordings revealed that evoked excitatory postsynaptic currents in red-labelled neurons were comparable to those in neighbouring green-labelled neurons. These currents were blocked by glutamate receptor antagonists, indicating that old and young mature granule cells received similar glutamatergic input from the entorhinal cortex. Likewise, inhibitory postsynaptic currents did not differ between neurons of different ages, suggesting similar GABA (γ-aminobutyric acid)-mediated afferent connectivity with interneurons.

Finally, the authors showed that firing behaviour in response to an excitatory stimulus was comparable in mature neurons born in adulthood and those born during development, indicating that excitatory input was integrated in a similar way in both types of neurons. Taken together, these results indicate that mature adult-born and perinatally born mouse hippocampal neurons have similar inhibitory/excitatory input balance and firing behaviours and in these respects form a homogeneous population.

By contrast, a second paper showed that, in rats, mature hippocampal neurons of different ages respond differently to certain behavioural conditions. Ramirez-Amaya *et al.* used high-resolution confocal microscopy to detect granule cells immunolabelled for ARC,

CANCER

Remodelling resistance



Patients with glioblastoma invariably fail to achieve long-term survival, which is thought to result from acquired resistance to chemotherapeutics or radiation, and is associated with the expression of transglutaminase 2 (TG2). Rich, Piwnica-Worms and colleagues show that small-molecule inhibitors of TG2 can overcome resistance to chemotherapy.

TG2 has many functions, including stabilizing fibronectin in the extracellular matrix (ECM). This is thought to enable the interaction of fibronectin with cellular integrins, setting up an anti-apoptotic cell–ECM signalling network that promotes glioblastoma cell survival. Indeed, the inhibition of TG2 in combination with the chemotherapeutic alkylating agent *N*,*N*′-bis(2-chloroethyl)-*N*-nitrosourea (BCNU) in a mouse glioblastoma xenograft model has previously been shown to increase apoptosis and reduce tumour weight. However, how the inhibition of TG2 activity sensitizes glioblastoma cells to chemotherapy remains unclear.

Using frozen anaplastic astrocytoma and glioblastoma samples, the authors show that TG2 activity and expression is significantly increased compared with normal brain tissue. The increased expression of TG2 in the ECM correlated with an abnormally dense linear assembly of fibronectin. Moreover, using fresh glioblastoma tissue they showed that TG2 and fibronectin are also overexpressed and abnormally organized in regions of the brain that have infiltrating tumour cells. So, is the abnormal expression of fibronectin functionally significant and caused by the increased expression of TG2? The authors show that the TG2 small-molecule inhibitor KCC009 prevents the assembly of fibronectin into dense strands along the cell surface of U87MG glioblastoma cells. Furthermore, mice with orthotopic glioblastoma (derived from injected DBT-bioluminescent glioblastoma cells) that were treated with KCC009 had reduced abnormal fibronectin expression that correlated with reduced TG2 activity. The relationship between fibronectin assembly and TG2 activity was also confirmed by RNA interference of TG2 in U87MG cells.

> “targeting factors that promote permissive remodelling of the ECM, such as TG2, could be a new approach to sensitizing glioblastoma cells to chemotherapy.”

Finally, the authors investigated whether KCC009 could sensitize DBT orthotopic tumours to BCNU. Using bioluminescence imaging, they showed

an immediate-early gene product which is produced in some neurons in response to exploration and is involved in long-term synaptic plasticity. The proportion of cells producing ARC after spatial exploration was higher in adult-born neurons than in perinatally born ones, indicating that neurons born in adulthood show enhanced plasticity when mature.

Keeping in mind that the two studies used different species and housing conditions, the data provide evidence that adult-born and perinatally born hippocampal neurons are integrated into similar neural networks, but might have different roles in spatial memory formation.

Leonie Welberg

ORIGINAL RESEARCH PAPERS
Laplagne, D. A. *et al.* Functional convergence of neurons generated in the developing and adult hippocampus. *PLOS Biol.* **4**, e409 (2006) | Ramirez-Amaya, V. *et al.* Integration of new neurons into functional neural networks. *J. Neurosci.* **26**, 12237–12242 (2006)
FURTHER READING Nithianantharajah, J. & Hannan, A. J. Enriched environments, experience-dependent plasticity and disorders of the nervous system. *Nature Rev. Neurosci.* **7**, 697–709 (2006)

that only KCC009 in combination with BCNU resulted in a significant reduction in tumour size. The tumours were analysed for levels of apoptosis, and mice treated with KCC009–BCNU combination therapy had higher levels of apoptosis than mice treated with each drug seperately. Similarly, monotherapy failed to increase the survival of the mice, unlike treatment with KCC009 and BCNU.

Remodelling the ECM is thought to provide a permissive environment for tumour growth. The authors suggest that KCC009 prevents the TG2-dependent remodelling of fibronectin, thought to function in pro-survival signalling in glioblastomas. Therefore, targeting factors that promote permissive remodelling of the ECM, such as TG2, could be a new approach to sensitizing glioblastoma cells to chemotherapy.

Gemma Alderton, Associate Editor,
Nature Reviews Cancer

ORIGINAL RESEARCH PAPER Yuan, L. *et al.* Transglutaminase 2 inhibitor, KCC009, disrupts fibronectin assembly in the extracellular matrix and sensitizes orthotopic glioblastomas to chemotherapy. *Oncogene* 13 Nov 2006 (doi:10.1038/sj.onc.1210048)

NEURODEGENERATIVE DISORDERS

Choice cuts?

Evidence for the key role of amyloid-β (Aβ) in Alzheimer's disease has led to considerable interest in potential therapeutic strategies targeting the two enzymes — β- and γ-secretase — that produce Aβ through sequential cleavage of the Aβ precursor protein. Three recent papers report findings that could have significant implications for these strategies.

In the first study, reported in *Nature Medicine*, Ni and colleagues sought to investigate how the pathogenesis of Alzheimer's disease is influenced by environmental factors such as stress, which is mediated by receptors including the β_2-adrenoceptor (β_2-AR). Using cell-based assays, they found that β_2-AR-activation increased the secretion of Aβ, which was blocked by pretreatment with a γ-secretase inhibitor. Subsequent experiments using an assay of the activity of γ-secretase indicated that the β_2-agonist-induced increase in Aβ secretion was due to increased γ-secretase activity.

Next, the authors probed the mechanism for enhanced γ-secretase activity. After finding that the activity enhancement was independent of cyclic AMP signalling, they discovered that endocytosis inhibitors or small interfering RNA against clathrin — a protein involved in the formation of endocytotic vesicles — abolished β_2-AR-induced γ-secretase activity. So, β_2-AR-induced enhancement of γ-secretase activity is dependent on clathrin-mediated endocytosis. Further experiments revealed that the β_2-AR directly associates with with presenilin 1 — the catalytic subunit of γ-secretase — which was trafficked to late endosomes and lysosomes where Aβ production was elevated.

Finally, Ni *et al.* studied the effects of β_2-AR activation in rodents. Administration of either noradrenaline or a selective β_2-AR agonist enhanced γ-secretase activity and hippocampal Aβ levels in rats. Mice with cerebral amyloid plaques chronically treated with a selective β_2-AR agonist showed increased plaques, whereas mice treated with a selective β_2-AR antagonist had reduced plaque levels.

Together, these results suggest a mechanism for the pathological role of stress in Alzheimer's disease, and indicate that β-AR antagonists — which have long been widely used in cardiovascular disease therapy — might have therapeutic potential for Alzheimer's disease. This idea is supported by a recent study suggesting that the use of β-AR antagonists correlates with a decreased incidence of Alzheimer's disease.

The other two papers, in *Science* and *Nature Neuroscience*, focus on the β-secretase enzyme, which in recent years has been viewed by some as a more promising target for reducing the pathological formation of Aβ than γ-secretase, in part owing to the role of γ-secretase in normal physiological processes. However, the physiological role of β-secretase has not been clear.

To investigate this role, both Willem *et al.* and Hu *et al.* used β-secretase-null (*Bace1*-null) mice. Lack of *Bace1* resulted in the accumulation of unprocessed neuregulin 1, which is required for glial cell development and myelination. Together, their results indicate that β-secretase has a crucial role in the myelination of peripheral and central nerves during development. Although it remains to be determined whether the influence of β-secretase is important in the maintenance of the mature myelin sheath, these studies suggest that β-secretase inhibition for Alzheimer's disease should be approached with caution.

Charlotte Harrison, Associate Editor,
Nature Reviews Drug Discovery

ORIGINAL RESEARCH PAPERS Ni, Y. *et al.* Activation of β_2-adrenergic receptor stimulates γ-secretase activity and accelerates amyloid plaque formation. *Nature Med.* 19 Nov 2006 (doi:10.1038/nm1485) | Willem, M. *et al.* Control of peripheral nerve myelination by the β-secretase BACE1. *Science* **314**, 664–666 (2006) | Hu, X. *et al.* Bace1 modulates myelination in the central and peripheral nervous system. *Nature Neurosci.* **9**, 1520–1525 (2006)