APOE4 impairs blood-brain barrier via cyclophilin A

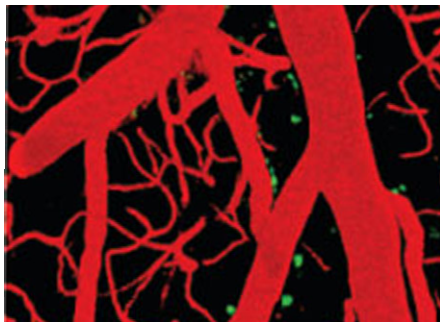

Image from Bell et al. (2012), with permission.

APOE4, a form of the human apolipoprotein E gene, is a genetic risk factor for Alzheimer's disease (AD) and is also associated with other forms of neuropathology. APOE4 is thought to compromise the blood-brain barrier (BBB), but the underlying mechanisms have been unclear. Bell et al. addressed this issue by studying the brain microvasculature in several strains of genetically engineered mice: one lacking the mouse *Apoe* gene, and others expressing human *APOE2*, *APOE3* or *APOE4*. They found that *Apoe*$^{-/-}$ and *APOE4* mice, but not *APOE2* or *APOE3* mice, had severe BBB defects that were caused by defective regulation of the levels of cyclophilin A (CypA). Increased levels of CypA in *Apoe*$^{-/-}$ and *APOE4* mice caused activation of NFκB, which in turn increased the expression and activation of MMP-9 in pericytes, which surround the microvasculature. Higher levels of active MMP-9 were shown to compromise BBB integrity in *Apoe*$^{-/-}$ and *APOE4* mice; notably, effects on the vasculature preceded neurodegeneration. Genetic ablation or pharmacological inhibition of CypA restored the BBB, as did an MMP-9 inhibitor. These results broaden our understanding of how APOE4 might compromise the BBB and thereby contribute to AD and other neuropathologies. *M.R.*

Bell, R. D., Winkler, E. A., Singh, I., Sagare, A. P., Deane, R., Wu, Z., Holtzman, D. M., Betsholtz, C., Armulik, A., Sallstrom, J. et al. (2012). Apolipoprotein E controls cerebrovascular integrity via cyclophilin A. *Nature* **485**, 512-516.

Neuronal regeneration: a role for apoptotic proteins

The ability to stimulate functional neuronal regeneration would markedly enhance treatment of brain injuries and neurodegenerative diseases. In studies of *C. elegans*, Pinan-Lucarre et al. uncovered unexpected roles for apoptotic proteins in promoting neuronal regeneration that might be conserved across species. Worms mutant for CED-3, the core executioner apoptotic protease in *C. elegans*, had slower axonal outgrowth and delayed neuronal reconnections after laser-mediated injury. The CED-3-activating protein CED-4 [homologue of mammalian apoptosis protease activating factor-1 (Apaf-1)], but not other upstream apoptotic proteins, was also important. They also linked CED-3 and CED-4 to a pathway involving DLK-1, a kinase implicated in regeneration across species. Finally, they showed that this regenerative pathway involves Ca^{2+} signalling (known to be important in neuronal responses to injury) and specifically the conserved Ca^{2+}-binding protein calreticulin. The authors propose a model whereby injury-induced Ca^{2+} signalling amplified by calreticulin promotes CED-4-mediated activation of CED-3, which then acts upstream of a DLK-1-mediated regenerative pathway. These data uncover a previously unknown pathway that will guide future studies of neuronal regeneration in higher organisms. *S.A.*

Pinan-Lucarre, B., Gabel, C. V., Reina, C. P., Hulme, S. E., Shevkoplyas, S. S., Slone, R. D., Xue, J., Qiao, Y., Weisberg, S., Roodhouse, K. et al. (2012). The core apoptotic executioner proteins CED-3 and CED-4 promote initiation of neuronal regeneration in *Caenorhabditis elegans*. *PLoS Biol.* **10**, e1001331. doi:10.1371/journal.pbio.1001331.

Selective requirement for glycine by cancer cells

Metabolic reprogramming is a hallmark of transformed cells, but knowledge of the specific pathways that are altered in cancer is still limited. To identify metabolic pathways commonly altered in multiple cancers, Jain, Nilsson et al. applied consumption and release (CORE) profiling to the NCI-60 cell lines (60 primary human cancer cell lines from nine tumour types). This led to the identification of glycine – a non-essential amino acid – as a metabolite that is consumed by rapidly growing cancer cells and released by slow-growing cancer cells. Glycine is endogenously produced in both the cytosol and mitochondria; using genetic profiling, the authors determined that transformed cells have an increased reliance on either exogenous glycine or glycine produced by the mitochondrial pathway. Analysis of existing transcriptome datasets from six independent cohorts of early-stage breast cancer patients showed that increased expression of genes associated with the mitochondrial glycine biosynthesis pathway is associated with increased mortality. Thus, glycine metabolism might be a promising therapeutic target in breast and possibly other types of cancer. *S.A.*

Jain, M., Nilsson, R., Sharma, S., Madhusudhan, N., Kitami, T., Souza, A. L., Kafri, R., Kirschner, M. W., Clish, C. B. and Mootha, V. K. (2012). Metabolite profiling identifies a key role for glycine in rapid cancer cell proliferation. *Science* **336**, 1040-1044.

Antidepressant responses: key cell type identified

Serotonin-specific reuptake inhibitors (SSRIs) are used to treat depressive disorders, which affect ~10% of the population. Improving treatment requires a better understanding of the molecular pathways affected by these agents in different brain-cell populations. Addressing this issue has been difficult owing to the interconnectivity and complexity of brain-cell populations. Schmidt and colleagues overcame this challenge by using a transgenic mouse model involving a bacTRAP translational profiling approach to investigate the role of the p11 protein in responses to SSRIs. p11 is known to maintain serotonin receptors at the cell surface and to mediate antidepressant responses; some studies indicate that its expression is decreased in the brains of those with depression. The researchers tracked cells that were actively translating p11 protein and characterised their response to SSRIs. On treating mice with an SSRI, p11 expression was upregulated in a specific subset of cells in the frontal cortex, the layer 5 corticostriatal projection neurons, and resulted in induced expression of *Htr4*, encoding a serotonin receptor. Genetic ablation of p11 in this cell type prevented the upregulation of *Htr4* and reduced the efficacy of SSRI treatment in mice. These data identify the cell type that is important in mediating the response to SSRIs, and provide unique mechanistic insight that might help to refine therapeutics for depression. *M.R.*

Schmidt, E. F., Warner-Schmidt, J. L., Otopalik, B. G., Pickett, S. B., Greengard, P. and Heintz, N. (2012). Identification of the cortical neurons that mediate antidepressant responses. *Cell* **149**, 1152-1163.