Identifying candidate ALS-associated genes in yeast

The tip of an iceberg in the Arctic Ocean near Norway, representing current knowledge about proteins involved in ALS. Image courtesy of Stanley H. Gitler, CPA.

Amyotrophic lateral sclerosis (ALS; also known as Lou Gehrig's disease) is a severely debilitating and fatal neurodegenerative disorder. The causes are largely unknown, and only ~10% of cases are due to familial genetic mutations. Some ALS-associated genes encode RNA-binding proteins and are prone to forming cytotoxic protein aggregates that contribute to pathology. To identify new disease-associated genes, Couthouis et al. designed a screen in yeast: they expressed 133 human proteins containing RNA-recognition motifs, and screened for those that caused cytoplasmic aggregates and reduced cell viability. Further analyses led to the identification of *TAF15* as a candidate. Sequencing analysis revealed *TAF15* missense mutations in several individuals with ALS, but not in healthy controls. Similar to the previously identified ALS-associated proteins FUS and TDP-43, disease-associated forms of TAF15 were shown to aggregate in cultures of primary spinal cord neurons and to cause neurodegeneration when expressed in *Drosophila*. These data indicate that FUS and TDP-43 might be just the tip of the iceberg with respect to the involvement of RNA-binding proteins in ALS. In addition, this study highlights the power of yeast functional screens to identify new disease-gene candidates. *M.R.*

Couthouis, J., Hart, M. P., Shorter, J., Dejesus-Hernandez, M., Erion, R., Oristano, R., Liu, A. X., Ramos, D., Jethava, N., Hosangadi, D. et al. (2011). A yeast functional screen predicts new candidate ALS disease genes. *PNAS* [Epub ahead of print] doi: 10.1073/pnas.1109434108.

Atherosclerosis: visualising oxidised LDL in zebrafish

Oxidation of low-density lipoprotein (LDL; the main vehicle for 'bad' cholesterol) is thought to contribute to the pathology of atherosclerosis in part by acting as a pro-inflammatory component of plaques. Antibodies specific for oxidised LDL (ox-LDL) have been used to visualise atherosclerotic lesions in mice and, when applied as a treatment, lessened signs of the disease through inhibiting the uptake of ox-LDL by macrophages. Fang et al. now apply these principles in zebrafish to develop an efficient system for testing new atherosclerosis therapies. Previously, the authors showed that zebrafish that were fed a high-cholesterol diet (HCD) exhibited pathological processes resembling early atherosclerosis in humans. In their new paper, they expressed an inducible and fluorescently labelled form of IK17, a monoclonal antibody specific for ox-LDL, in HCD-fed zebrafish to enable visualisation of ox-LDL in vivo. Vascular accumulation of ox-LDL decreased when HCD-fed zebrafish were switched to a normal diet, or following exposure to probucol, a potent antioxidant. Constitutive IK17 expression impaired ox-LDL binding by macrophages and markedly inhibited vascular ox-LDL accumulation in vivo. These data suggest that early treatment with ox-LDL-specific antibodies might be a viable therapy in humans with the disease. *S.A.*

Fang, L., Green, S. R., Baek, J. S., Lee, S. H., Ellett, F., Deer, E., Lieschke, G. J., Witztum, J. L., Tsimikas, S. and Miller, Y. I. (2011). In vivo visualization and attenuation of oxidized lipid accumulation in hypercholesterolemic zebrafish. *J. Clin. Invest.* [Epub ahead of print] doi:10.1172/JCI57755.

Functionally repairing complex synaptic circuitry

The complexity of neuronal circuits presents a challenge when investigating potential future treatments for diseases caused by central nervous system defects. In a highly collaborative study from three groups at Harvard Medical School, Czupryn et al. show that transplanted neurons can establish neuronal circuitry in the mouse hypothalamus. This brain region controls aspects of whole-body metabolism, such as satiety and energy expenditure, in part by interpreting signals from the adipocyte-derived hormone leptin. To assess the potential to functionally repair complex neuronal circuitry, the authors transplanted fluorescently labelled leptin-responsive immature neurons and progenitors into db/db mice (which lack the leptin receptor, and are thus severely diabetic and morbidly obese). The transplanted cells localised to the hypothalamus, differentiated into the appropriate neuronal subtypes necessary for leptin signalling, functionally integrated, and led to amelioration of obesity and hyperglycemia. Thus, transplanted neurons can establish complex neural circuitry and restore defective physiological functions, suggesting great therapeutic potential for selected nervous system diseases. *M.R.*

Czupryn, A., Zhou, Y. D., Chen, X., McNay, D., Anderson, M. P., Flier, J. S. and Macklis, J. D. (2011). Transplanted hypothalamic neurons restore leptin signaling and ameliorate obesity in db/db mice. *Science* **334**, 1133-1137.

Two routes to autism phenotypes via mGluR5

Fragile X syndrome (FXS) and tuberous sclerosis complex (TSC) are both associated with autism and intellectual disability, and are both caused by mutations that disrupt synaptic protein synthesis. However, a recent study by Auerbach et al. found that the two diseases are caused by an opposing mechanism. Previous work showed that mutant phenotypes in *Fmr1*$^{-/y}$ mice, a model of FXS, are minimised by reducing signalling by mGluR5 (a receptor for the excitatory neurotransmitter glutamate). Conversely, the new study showed that, in *Tsc2*$^{+/-}$ mice (a model of TSC), the same effect was achieved by potentiating mGluR5 signalling. Furthermore, crossing *Fmr1*$^{-/y}$ and *Tsc2*$^{+/-}$ mice produced a strain that is indistinguishable from wild type with regards to hippocampus-dependent synaptic plasticity and cognitive function, as the mutations cancelled one another out. These results expand knowledge about synaptic defects causing FXS and TSC, and highlight the fact that information on the underlying disease mechanisms is required to provide appropriate treatment. *J.H.*

Auerbach, B. D., Osterweil, E. K. and Bear, M. F. (2011). Mutations causing syndromic autism define an axis of synaptic pathophysiology. *Nature* [Epub ahead of print] doi:10.1038/nature10658.