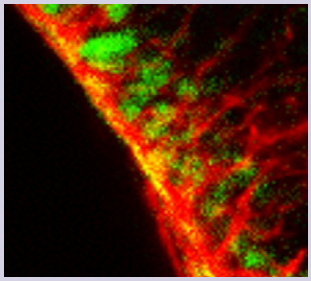


Neuronal regeneration in a zebrafish model of brain injury

Traumatic brain injury (TBI) is the most common type of brain injury. Therapies that stimulate endogenous neural stem cells might enable regeneration of damaged neural tissue, but the mechanisms by which these cells can be activated are not clear. Kishimoto et al. use a zebrafish model of TBI and in vivo imaging to show that neural precursor cells in the adult tencephalon proliferate following brain injury, migrate towards the lesion site and differentiate into mature neurons in a Notch1-pathway-dependent manner. This model can be used to further elucidate pathways that could be targeted to induce neural repair in humans affected by TBI. **Page 200**

New zebrafish model for maple syrup urine disease

Maple syrup urine disease (MSUD) is a rare inherited disorder involving defects in the metabolism of branched-chain amino acids. Effects of the resulting by-products on the central nervous system (CNS) can lead to mental retardation, dystonia and death. Friedrich et al. report a zebrafish mutant (*que*) with characteristics resembling human MSUD, including increased levels of branched-chain amino acids, CNS defects and abnormal behaviour. The mutation is mapped to *dbt*, a homologue of human *DBT*, in which mutations have been associated with MSUD. The *que* mutant should help to better understand the mechanisms causing brain injury in individuals with MSUD and aid in the development of new therapies. **Page 248**

Effects of metformin on cardiomyocytes

Recent clinical data suggest that individuals with type 2 diabetes (T2D) that receive metformin as a treatment suffer fewer T2D-associated cardiac complications. Quentin et al. set out to determine how metformin acts on the heart by studying rat cardiomyocytes. They focus on endoplasmic reticulum stress signalling (ERSS) pathways, which have previously been shown to be involved in both heart disease and T2D. They find that metformin activates only one of three ERSS pathways – the PERK-ATF4 pathway, leading to induction of CHOP. CHOP is usually proapoptotic, but metformin-treated cardiomyocytes do not activate apoptotic signalling pathways nor undergo apoptosis. The authors propose that future studies of T2D drugs should consider ERSS pathways. **Page 259**

Probing pathomechanisms of mucolipidosis II in fish

Mucolipidosis II (MLII) is a rare lysosomal storage disorder causing diverse clinical symptoms such as skeletal and craniofacial defects and heart abnormalities. Petrey et al. probe the molecular mechanisms underlying craniofacial defects that are recapitulated in a zebrafish model of MLII they developed previously. Analysis of chondrocyte-enriched populations shows that zebrafish MLII embryos have increased activity of several enzymes involved in remodelling of the extracellular matrix, particularly cathepsins L and K and matrix metalloproteinase 13. Exposure of MLII embryos to a cathepsin K inhibitor lessens the disease phenotype. These data pinpoint new players in MLII that will guide further studies of the disease. **Page 177**

iPSC-derived model of long QT syndrome

Long QT syndrome (LQTS) is a cardiac disorder associated with ventricular arrhythmias and sudden death. It can be caused by genetic defects or as a side effect of drugs, in both cases involving impairment of the hERG potassium channel. Lahti et al. developed a model involving cardiomyocytes differentiated from human induced pluripotent stem cells (iPSCs) and tested whether LQTS-associated phenotypes could be detected in vitro. Surprisingly, iPSC-derived cardiomyocytes from an asymptomatic carrier of a *HERG* mutation have an abnormal phenotype. These findings could be applied to assess cellular defects of individuals with LQTS, and suggest that asymptomatic carriers of mutations affecting hERG function have an increased risk of being adversely affected by certain drugs. **Page 220**

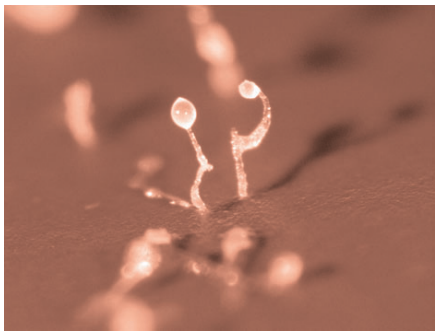
Batten disease: lipid transport goes awry

Batten disease is a childhood neurodegenerative disorder caused by defects in the lysosomal membrane protein CLN3. To probe how defective CLN3 function causes disease, Padilla-López et al. investigate the role of the yeast homologue, Btn1p, in intracellular lipid transport. They find that *BTN1* deletion disrupts trafficking of essential lipids from the endoplasmic reticulum to mitochondria and vacuoles (the yeast equivalents of mammalian lysosomes), and also impairs the Kennedy pathway, which synthesises essential lipids. Thus, defects in *BTN1* – and by extension its human homologue *CLN3* – might disrupt intracellular lipid transport, causing pleiotropic effects on cellular function that contribute to the pathology of Batten disease. **Page 191**

PTEN haploinsufficiency and hemangiosarcoma

PTEN negatively regulates phosphoinositide 3-kinase (PI3K) signalling and is frequently mutated in human cancers. Because complete deletion of PTEN is embryonic lethal in most model organisms, studying its biological role has been challenging. Choorapoikayil et al. studied the consequences of reduced PTEN expression using mutant zebrafish (which naturally express two functional Pten genes). They find that zebrafish lacking three of the four normal Pten alleles are viable but develop hemangiosarcomas (aggressive tumours of blood vessel origin), mainly close to the eye. These data introduce a new zebrafish model of hemangiosarcoma and expand knowledge on the role of PTEN in endothelial cells. **Page 241**

Assessing hepatotoxicity of valproic acid in *Dictyostelium*



Valproic acid (VPA) is commonly prescribed for epilepsy, bipolar disorder and migraine, despite side effects such as fatty liver (hepatic steatosis). Elphick et al. use the social amoeba *Dictyostelium* to investigate the mechanisms underlying the drug's adverse effects; in particular, how it induces intracellular lipid-droplet accumulation. Their results suggest that VPA and structurally related compounds inhibit fatty acid β-oxidation. The compounds have similar effects in human hepatocytes, suggesting that *Dictyostelium* is a viable model for structure-activity-based screens of VPA-related compounds aiming to develop improved drugs with fewer side effects. **Page 231**

Cdk5 deficiency and neurodegeneration in flies

Cdk5 is thought to be involved in several neurodegenerative diseases, but whether it provides protection or propagates pathology has been unclear. Trunova and Giniger address this issue using mutant flies in which Cdk5 is inactive. These flies show adult-onset neurodegeneration with specific effects on mushroom bodies, the regions of the fly brain that govern learning and memory. Mutant flies also exhibit other cellular phenotypes that resemble those seen in human neurodegenerative disease. This model can be used to separate processes associated with aging from those that specifically contribute to neurodegeneration caused by decreased Cdk5 function. **Page 210**

Profiling gene expression during cerebral ischemia

Cerebral ischemia caused by occlusion of blood flow causes damage to brain tissue, leading to severe neurological and psychological symptoms or even death if not resolved quickly. Hori et al. use a whole-genome DNA microarray approach to characterise the molecular events of an ischemic episode in mice. The data confirm previous findings that inflammatory pathways are activated, but also show an up- or downregulation in the expression of many genes not previously associated with cerebral ischemia. This study provides new candidate genes and pathways for cerebral ischemia, as well as clues about endogenous factors that might prevent or reverse tissue damage. **Page 270**

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