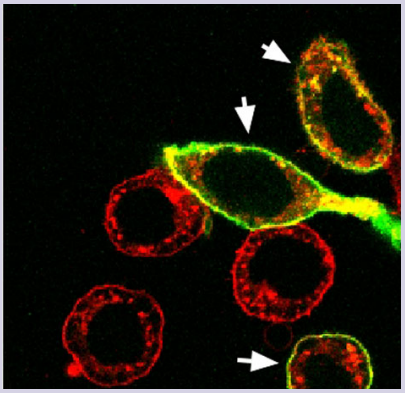

Exposing *H. pylori* virulence mechanisms

Persistent stomach infection with the bacterium *Helicobacter pylori* is associated with gastric ulcers and cancer. To gain further insight into the pathology of these diseases, Akada et al. explore the relationship between two main *H. pylori* virulence factors – CagA and VacA – using genome-wide screening in yeast and validation experiments in human gastric epithelial cells. The data suggest that *H. pylori* injects CagA into the host cells to which it is attached, inhibiting clathrin-independent endocytosis, preventing the entry of highly cytotoxic VacA into the cells. Instead, secreted VacA might damage distant host cells. This functional antagonism between CagA and VacA allows *H. pylori* to create a niche for persistence by protecting cells in the immediate microenvironment. *S.A.*

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All research articles are freely accessible online.

Galactose disorders modelled in flies

Classic galactosemia and generalised epimerase deficiency galactosemia are caused by defects in key enzymes, GALT and GALE, respectively, responsible for the metabolism of dietary galactose. Both disorders can have severe effects, in extreme cases leading to neonatal death, and their prognosis and treatment remain problematic, partly due to lack of a good animal model. Judith Fridovich-Keil and colleagues present data in two linked papers describing Drosophila models for loss of GALT and GALE, and demonstrate that important aspects of the human disease phenotypes are also found in flies. *K.W.*

Pages 618 and 628

Stress signals provoke β-cells

In diabetic patients, insulin-producing islet β-cells responsible for maintaining normal blood-glucose levels are often damaged or destroyed. Given the therapeutic potential for regenerating healthy β-cells, there is interest in understanding the pathways that regulate their expansion and response to metabolic stress. Villasenor et al. now show that the expression of two regulators of G-protein signalling, Rgs16 and Rgs8, is induced by chronic glucose stress in pancreatic endocrine cells in various mouse models. These are sensitive reporters of metabolic change and might influence the regeneration of β-cells in mature and developing tissue. *K.K.*

Page 567

A zebrafish model for ALS

Amyotrophic lateral sclerosis (ALS) is a devastating and incurable neuromuscular disease. Identification of its causes, and development of effective treatments and drugs, are urgent priorities. Ramesh et al. describe a new zebrafish model, based on mutation of superoxide dismutase (SOD1), which recapitulates many aspects of the disease and should provide a powerful weapon for both basic research and drug discovery. *K.W.*

Page 652

Two-pronged approach to studying copper metabolism

Copper is an essential nutrient, and deficiency can result in hypopigmentation and neuronal or muscular problems. Deficiency can result from mutations in the copper transporter ATP7A (as in Menkes disease), but many other causes are unknown. Ishizaki et al. take a combined approach to probe biological pathways that are sensitive to copper depletion: they use a zebrafish-based chemical screen to identify compounds affecting copper metabolism, and a yeast genetic screen to map the genetic pathways underlying responsiveness to the compounds. Their results indicate that hypomorphic alleles encoding intracellular trafficking components might underlie sensitivity to reduced copper availability. In addition, this study highlights how disease susceptibility can be influenced by gene-environment networks. *S.A.*

Page 639

Amyloid processing in Dictyostelium

Improper processing of amyloid precursor protein (APP) in the brain gives rise to β-amyloid plaques, a hallmark of Alzheimer's disease (AD). Familial forms of AD often arise from changes in proteins that regulate APP processing, such as γ-secretase, which cleaves APP and other type I transmembrane proteins. McMains et al. identify γ-secretase in Dictyostelium that – although highly diverged from human γ-secretase – precisely cleaves human APP. So, Dictyostelium, a primitive eukaryote that is easy to study, might be a useful model to understand γ-secretase function in the context of familial mutations associated with AD. *K.K.*

Page 581

RANBP2 and cell-type-specific neuroprotection

Oxidative stress contributes to ageing and to the pathology of many human diseases. Identifying factors that inhibit the effects of oxidative stress in neurons might help to develop therapies for neurodegenerative diseases, including retinal dystrophies. Cho et al. now show that the neuroprotective effect of RANBP2 insufficiency is cell-type specific: analyses of *RANBP2*-haploinsufficient mice show that photoreceptors are protected from light-induced oxidative stress, owing to altered protein homeostasis, whereas the supporting retinal pigment epithelium has altered lipid homeostasis. *S.A.*

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