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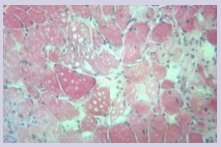


Promoting skeletal muscle regeneration in mouse and fly models of DMD

Duchenne muscular dystrophy (DMD) causes progressive muscle weakness. There is currently no cure for the disease; however, recent studies have suggested that a bioactive lipid, sphingosine-1-phosphate (S1P), might protect against eventual muscle degeneration. S1P is an inhibitor of histone deacetylases (HDACs), which could form the molecular basis of its protective role in DMD. To test this possibility, Hannele Ruohola-Baker and colleagues exploited *Drosophila* and mouse models of the disease. They reduced levels of Rpd3, the *Drosophila* homologue of HDAC2, and found that disease symptoms were alleviated. In DMD mice, symptoms were also improved upon treatment with a compound that increases levels of S1P and suppresses HDAC activity. Interestingly, this improvement correlated with the expression of two miRNAs involved in promoting regeneration and energy metabolism in skeletal muscle tissue. This cross-species analysis thereby provides important insights into the pathology of DMD and the therapeutic potential of S1P. Page 41

Drug discovery for neutrophil-mediated inflammation

Neutrophils are key cells of the innate immune system, the first line of defense against infection. However, neutrophils can drive a chronic inflammatory response that underlies the pathogenesis of many common diseases, including chronic obstructive pulmonary disease and inflammatory bowel disease. Despite the prominence of neutrophil-mediated inflammation in disease, there are no suitable neutrophil-targeted treatments currently available. A new report from the laboratories of Stephen Renshaw and Philip Ingham describes a novel approach for the rapid identification of compounds that can inhibit neutrophil recruitment in response to tissue injury *in vivo*. Using a zebrafish line in which neutrophils are labelled by GFP expression, the team screened a library of fungi-derived compounds and pinpointed a mycotoxin and a natural antibiotic with specific inhibitory effects on neutrophil migration. An *in vivo* imaging assay showed that the antibiotic acts independently of commonly implicated signalling pathways, suggesting an unanticipated mechanism of action. This work demonstrates that zebrafish can be used as a robust *in vivo* platform for high-throughput drug discovery. Page 163

A nutrient-sensing pathway activated in APC-driven colorectal cancer

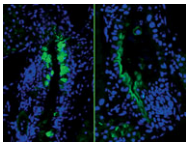
Truncating mutations in the tumour suppressor gene encoding APC are the most common cause of colorectal cancer. APC is a negative regulator of the Wnt signalling pathway, and constitutive activation of Wnt–β-catenin signalling is thought to form the basis of the oncogenic effects of *APC* mutations. However, recent evidence has suggested that other proteins could also be involved. Alexander Valvezan, Peter Klein and colleagues recently showed that APC suppresses mTORC1 activity *in vitro*. Here, the group explored the relationship between APC and mTORC1, a nutrient sensor that regulates cell growth and proliferation, *in vivo*. The authors show that mTORC1 activity is markedly upregulated in *apc* mutant zebrafish and in intestinal polyps in *Apc* mutant mice. mTORC1 inhibition suppressed multiple developmental defects caused by *apc* mutation in zebrafish. Interestingly, combined inhibition of mTORC1 and Wnt signalling was needed to restore normal body curvature. These findings suggest that mTORC1 is a key mediator of *APC*-driven tumorigenesis and developmental defects, and suggest mechanistic overlap with other polyposis syndromes that are associated with mTORC1 activation. Page 63

A combinatorial therapy for treating obesity

Obesity is quickly becoming a worldwide epidemic, and there are currently no effective therapies. Despite their promise, early treatment strategies failed to demonstrate clinical efficacy, which has prompted researchers to focus on the development of combinatorial therapies. Some of the earlier strategies relied on stimulation of β3-adrenergic receptors, and there is recent evidence that the effect of β3-adrenergic activation could be potentiated by combining it with PPARβ-receptor activation. To explore this possibility *in vivo*, Fernando Rodríguez de Fonseca and colleagues subjected rats to co-treatment with a β3-adrenergic agonist and a PPARβ-activating ligand. This had an effect on multiple processes involved in energy balance, including feeding, thermogenesis and fatty acid oxidation, promoting an overall increase in energy expenditure and decrease in energy intake. These results suggest that pharmacological combination of PPARβ and β3-adrenergic receptor agonists could represent a promising therapy for treating obesity. Page 129

A protective role for the UPR in galactosaemia

Galactosaemia is a rare metabolic disorder characterised by the inability to properly metabolise galactose, a breakdown product of lactose. This leads to toxic accumulation of a precursor metabolite, galactose-1-phosphate (Gal-1-P), which causes liver problems and failure to thrive, as well as long-term developmental consequences if left untreated. The molecular basis of galactose toxicity has remained poorly understood; however, insights are provided in new research from Claudio Masuda and colleagues. Using established yeast models of galactosaemia, they demonstrate that the unfolded protein response (UPR), a cellular response to ER stress, is upregulated in galactosaemic conditions. Upregulation of the UPR is dependent on Gal-1-P synthesis, and impairment of the response makes cells even more vulnerable to cytotoxicity. These results highlight the importance of ER stress in mediating the toxic effects of galactose, and suggest that the UPR plays a protective role that could be harnessed in novel treatments for galactosaemia. Page 55



Phosphatidylinositol signalling defects implicated in IBD

Inflammatory bowel disease (IBD), the collective term for a group of chronic conditions characterised by inflammation of the gastrointestinal tract (including Crohn's disease and ulcerative colitis), affects an estimated 1.4 million individuals in the US, and its incidence is increasing worldwide. Current treatments generally manage the symptoms rather than provide a cure, highlighting the need to develop effective molecular therapies. In this new study, Nathan Bahary and colleagues use zebrafish to demonstrate that a deficiency in phosphatidylinositol (PI) signalling could be involved in the pathogenesis of IBD. Abnormalities in PI signalling have been linked with gastrointestinal disorders; however, the mechanisms remained unclear. Here, the authors show that PI-synthesis-deficient zebrafish display persistent ER stress and disrupted intestinal architecture, resulting in IBD-like pathologies. These effects can be mimicked by pharmacological induction of ER stress, whereas abrogation of ER stress using chemical chaperones rescues the disease phenotype. These findings link PI signalling defects with ER-stress-mediated gastrointestinal disease, revealing a mechanism that could be targeted in the development of curative therapies for IBD. Page 93