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Polyunsaturated fatty acids: an alternative to statins for treating heart disease?

Cardiovascular diseases (CVDs) are a group of common, debilitating conditions that can be fatal without treatment. Build-up of lipid in the arteries (atherosclerosis) is associated with increased risk of CVD, so lowering serum cholesterol is a major therapeutic route. This is achieved by administration of statins, which inhibit endogenous cholesterol synthesis. Although this therapy is effective, its use is limited in some cases because of side effects. Here, Amnon Schlegel and colleagues bring to light a possible alternative to statins for the treatment of CVD. Using a zebrafish model, they demonstrate that coenzyme-A-activated polyunsaturated fatty acids (PUFA-CoAs) can inhibit cholesterol synthesis. In support of this finding, they show that PUFA-CoAs can directly inhibit the human enzyme for cholesterol synthesis *in vitro*, and also have an inhibitory effect in mice. Thus, fish oil supplements that contain polyunsaturated fatty acids could represent a new therapeutic candidate for lowering blood cholesterol. This intriguing possibility now awaits confirmation in a clinical setting. **Page 1365**

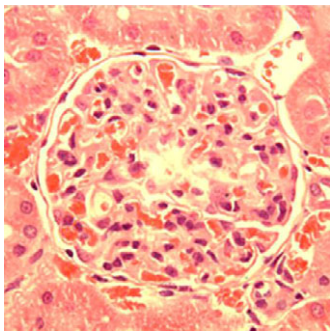
A reliable mouse model for studying intestinal epithelial damage

Inflammation of the intestinal epithelium is a common feature of many acute and chronic gastrointestinal disorders, including Crohn's disease. Damage to the intestinal lining is thought to be mediated by increased shedding of epithelial cells and enhanced gut permeability. These processes remain poorly understood at the molecular level, in part because of a lack of suitable animal models. Now, Mark Pritchard and colleagues have established a robust model for examining intestinal epithelial cell shedding, using lipopolysaccharide (LPS) treatment to induce intestinal injury in mice. They show that LPS-treated mice develop diarrhoea, which correlates with intestinal epithelial cell shedding and caspase-3-driven apoptosis. By examining the effects of LPS in knockout mice, they demonstrate a role for TNFR1 and NFκB2 signalling in these molecular events. The model provides a powerful tool for investigating the mechanisms underlying intestinal epithelial damage, which could guide the development of new therapies for gastrointestinal disorders. **Page 1388**

A new druggable target for clinical management of COPD

Exposure to tobacco smoke and environmental pollutants can cause chronic obstructive pulmonary disease (COPD), a severe lung disease characterised by progressive breakdown of lung tissue (emphysema). COPD is a leading cause of death worldwide and is described as a global epidemic. SESN2, an antioxidant protein, has been implicated in genetically determined emphysema. To find out if this protein is also involved in COPD pathogenesis, Harald von Melchner and colleagues knocked out *Sesn2* in a mouse model of cigarette-smoke-induced pulmonary emphysema. They discovered that inactivation of *Sesn2* protects mice from the disease. Furthermore, they demonstrate that protection is mediated by upregulation of PDGFRβ signalling, which has a role in the maintenance of alveoli. The importance of SESN2 in disease pathogenesis is supported by the group's finding that SESN2 is overexpressed in the lungs of humans with advanced COPD. These results implicate SESN2 as a key biomarker and potential therapeutic target in the clinical management of COPD. **Page 1378**

Insights into kidney disease using a bicongenic rat model



Crescentic glomerulonephritis (CRGN) is a rapidly progressing kidney disease characterised by crescent-shaped scars on the glomeruli. The disease can cause potentially fatal renal failure. Experimental rat strains have been used to study CRGN at the molecular level, and this has allowed two key susceptibility loci to be mapped. One of the commonly used strains is susceptible to induction of CRGN, whereas another is resistant, allowing the effects of the susceptibility loci in different genetic backgrounds to be determined. Here, Timothy Aitman's group establish a new bicongenic rat model in which both susceptibility loci are introgressed into the resistant strain. Interestingly, the resulting rats display macrophage-dependent CRGN in response to injection by nephrotoxin; however, they remain resistant to glomerulonephritis induced by serological autoimmunity. This work thereby provides a novel model for the study of macrophage-dependent CRGN, and also paves the way for elucidation of the mechanisms underlying susceptibility to different forms of the disease. **Page 1477**

Cre-recombinase-associated toxicity highlights limitations of genome editing

Bacterial endonucleases have become powerful tools for mammalian genome editing, and new technologies such as TALENs and CRISP/Cas9 are increasingly used in biomedical research. However, unwanted 'off-target' effects of these nucleases could limit their usefulness. The Cre-*loxP* site-specific recombination system is a long-established tool for genetic manipulation, yet recent research has suggested that this approach could also lead to adverse effects. Cre activity, which is induced in response to tamoxifen treatment, has been frequently exploited in

mouse models of heart disease to investigate the effects of knocking out disease-associated genes in specific cardiac cells. Two articles published in this issue report results of investigations into Cre-recombinase-associated toxicity in mouse cardiac tissue. Nadia Rosenthal's group systematically characterised the effects of Cre activity on cardiac morphology, physiology and function (**page 1470**). Their analysis revealed that a significant proportion of treated mice develop cardiac fibrosis in response to Cre activity. Interestingly, the severity of the phenotype varied in different genetic backgrounds, and toxicity was dependent on the frequency of tamoxifen injections. In the second study, Bernhard Kühn and colleagues substantiate these findings by demonstrating that Cre activity leads to cardiac toxicity and cardiomyocyte apoptosis in a dose-dependent manner (**page 1459**). Importantly, both studies ruled out the possibility that toxicity is caused by tamoxifen rather than Cre activity. Collectively, these analyses confirm that the Cre-*loxP* system can have unwanted, toxic effects in target tissue, highlighting the need for careful experimental design in studies utilising this tool and related genome-editing technologies.