GENETIC DISEASES

New tricks for known drugs

Two recent papers have identified novel potential treatments for liver disease and kidney disease based on compounds that have already been in clinical trials for other disorders.

In the first study, reported in *Nature Medicine*, Natoli and colleagues show that an inhibitor of glucosylceramide synthase has beneficial effects in models of polycystic kidney disease (PKD), a group of genetic disorders that are characterized by defects in renal cystic epithelia, cystic growth and the progression to kidney failure. Because changes in glycosphingolipid metabolism are thought to drive cyst growth, the authors proposed that lowering glucosylceramide levels might be effective in PKD. To achieve this, they used Genz-123346, an orally available inhibitor of glucosylceramide synthase, which shares structural features with previously developed inhibitors that were well tolerated in Phase II trials for Gaucher's disease.

Genz-123346 inhibited renal cystogenesis in various mouse models of PKD. In models representative of human juvenile and adult nephronophthisis — *jck* and *pcy* mice, respectively — Genz-123346 treatment reduced glucosylceramide and ganglioside GM3 levels, and inhibited cystic disease. Similar results were also observed in *Pkd1* conditional knockout mice, a model considered to be orthologous to human autosomal dominant PKD.

Next, the authors investigated the molecular targets affected by glycosphingolipid modulation in the cystic kidney. Genz-123346 had a direct effect on the cell cycle machinery, suggesting that it caused G1/S cell cycle arrest. Furthermore, it inhibited cellular proliferation and modulated the AKT–mTOR signalling pathway. Chronic treatment also indirectly inhibited apoptosis and MEK–ERK signalling. Of note, Genz-123346 had no effect on pathways in the kidneys of wild-type mice, suggesting its effect is limited to the diseased kidney. Together, these results show that modulation of glycosphingolipid metabolism could be a new approach for the treatment of PKD.

In the second paper, published in *Science*, Hidvegi and colleagues show how carbamazepine, a drug currently used as an anticonvulsant and a mood stabilizer, could have beneficial effects in genetic liver disease. The most common genetic cause of liver disease in childhood is the deficiency of α1-antitrypsin, which can also present with cirrhosis and/or hepatocellular carcinoma in adulthood. The condition is characterized by accumulation of an aggregation-prone α1-antitrypsin mutant — known as ATZ — inside cells. Because autophagy is involved in the degradation of ATZ and in the cellular response to the accumulation of ATZ, the authors tested whether carbamazepine, which is known to enhance autophagy, could ameliorate the hepatotoxicity associated with liver disease.

Results from cell-based studies suggested that carbamazepine exerts its effects by changing the rate of intracellular degradation of insoluble ATZ. This change occurs through increasing the stimulation of autophagy in cells that already have an activated autophagic pathway in response to the accumulation of ATZ. In addition, carbamazepine enhanced the disposal of soluble ATZ through mechanisms that do not involve the conventional autophagic pathway.

Next, the authors examined the effect of carbamazepine on the hepatic load of ATZ in a mouse model of liver disease associated with α1-antitrypsin deficiency. Administration of carbamazepine decreased total, insoluble and soluble ATZ in the liver, and also decreased intrahepatocytic ATZ-containing globules and increased hepatic autophagosomes. In models of hepatic fibrosis — a key feature of α1-antitrypsin deficiency — the drug decreased fibrosis and liver damage. These results provide the rationale for studies of carbamazepine in patients with α1-antitrypsin deficiency and highlight the fact that autophagy enhancers could also be used in other conditions characterized by gain-of-toxic function mechanisms caused by misfolded proteins or aggregation-prone proteins.

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ORIGINAL RESEARCH PAPERS Natoli, T. A. *et al.* Inhibition of glucosylceramide accumulation results in effective blockade of polycystic kidney disease in mouse models. *Nature Med.* 20 Jun 2010 (doi:10.1038/nm.2171) | Hidvegi, T. *et al.* An autophagy-enhancing drug promotes degradation of mutant α1-antitrypsin. *Science* 3 Jun 2010 (doi: 10.1126/science.1190354)