IN BRIEFS

CHEMICAL LIBRARIES

Encoded self-assembling chemical libraries.

Melkko, S. *et al*. *Nature Biotechnol.* 18 April 2004 (doi:10.1038/nbt961)

The isolation of molecules capable of high-affinity and specific binding to biological targets is a central problem in drug discovery. This paper describes the use of encoded self-assembling chemical (ESAC) libraries for the identification of molecules that bind macromolecular targets. ESAC technology uses libraries of organic molecules linked to individual oligonucleotides that mediate the self-assembly of the library and provide a code associated with each organic molecule. After panning ESAC libraries on the biomolecular target of interest, the 'binding code' of the selected compounds can be 'decoded' by a number of experimental techniques. This technology was demonstrated by the affinity maturation (>40-fold) of binding molecules to human serum albumin and bovine carbonic anhydrase.

INFLAMMATORY BOWEL DISEASE

Functional variants of OCTN cation transporter genes are associated with Crohn's disease.

Peltekova, V. D. *Nature Genet.* 11 April 2004 (doi:10.1038/ng1339)

Genetic variation in DLG5 is associated with inflammatory bowel disease.

Stoll, M. *Nature Genet.* 11 April 2004 (doi:10.1038/ng1345)

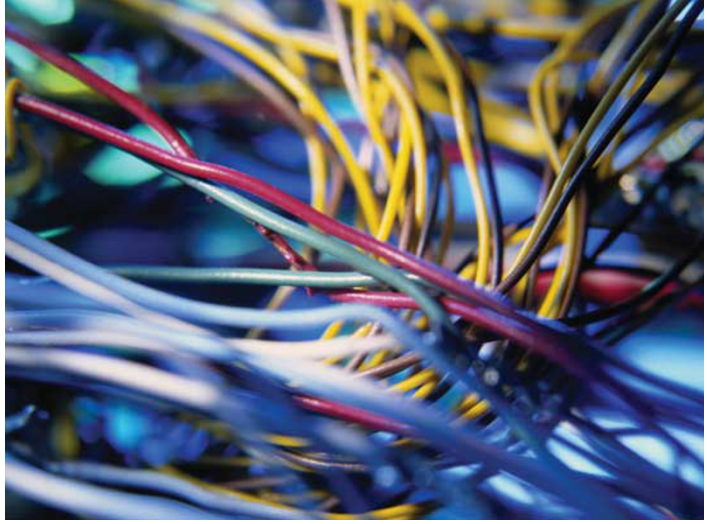
Two recent studies have identified genes associated with susceptibility to the inflammatory bowel diseases Crohn's disease (CD) and ulcerative colitis (UC). Variants of two neighbouring genes on chromosome 5 are associated with susceptibility to CD. These genes encode related proteins whose function is to transport small molecules across cell membranes. The variant of one of the genes results in a protein with altered transport properties; the other variant alters a binding site for a factor that controls expression levels of the second gene. A different gene on chromosome 10 is associated with susceptibility to both UC and CD. This gene encodes a protein involved in maintaining the integrity of cellular sheets like the one that forms the lining of the intestine.

ANTIBACTERIAL DRUGS

Structural insight into arginine degradation by arginine deaminase, an antibacterial and parasite drug target.

Galkin, A. *et al*. *J. Biol. Chem.* **279**, 14001–14008 (2004)

L-Arginine deaminase (ADI) is involved in the first step of the most widespread anaerobic route of arginine degradation. Its important function in both pathogenic protozoa and bacteria, in addition to its absence in higher eukaryotes, make the enzyme an attractive therapeutic target for the treatment of bacterial and parasitic infections. The crystal structure of ADI from *Pseudomonas aeruginosa* has been solved at 2.45 Å resolution. On the basis of the structure, the authors propose an ADI catalytic mechanism.



NEURODEGENERATIVE DISEASE

Metabolite-mediated misfolding

The three-dimensional conformation of a protein is in large part specified by its amino-acid sequence, so mutations can lead to aberrant folding. But why do normal, mutation-free proteins become misfolded? Resolving this conundrum would improve our understanding of the sporadic form of Alzheimer's disease, in which wild-type amyloid β-peptides (Aβ) misfold and aggregate to form pathogenic plaques in the brain.

One possibility is that modification by abnormal metabolites causes wild-type Aβ to misfold. Recently established links between Alzheimer's disease, high cholesterol levels and inflammation prompted a team of investigators led by Jeffery Kelly to focus on the Aβ-modifying potential of metabolites that form through the reaction of cholesterol with ozone, which is generated during inflammation.

A key property of these cholesterol metabolites is that they possess an aldehyde group, which could form a bond with amines in Aβ. Attachment of cholesterol metabolites would markedly increase the hydrophobicity of Aβ, potentially increasing the likelihood of misfolding. To assess this possibility, several cholesterol metabolites were individually incubated with Aβ. Two — dubbed compounds 1 and 2 — caused a concentration-dependent increase in the rate of amyloidogenesis and were shown to be present in human brains.

Once formation of aggregates in the *in vitro* assay had ceased, the authors measured the amount of soluble Aβ that remained in the reaction mixture. This provided an estimate of the 'critical concentration' for aggregation in the presence of compound 1 or 2. The derived maximal value of 90 nM is much lower than that for metabolite-free Aβ (reported as being ~15 μm), which might explain why physiological concentrations of Aβ (typically in the nanomolar range) result in the formation of amyloid plaques in individuals lacking predisposing mutations. Bringing the evidence from this and other studies together, the authors suggest that atherosclerosis-related inflammation causes ozonolysis of cholesterol, transiently increasing the concentrations of highly reactive metabolites that in turn initiate amyloidogenesis.

Suzanne Farley

References and links

ORIGINAL RESEARCH PAPER Zhang, Q. *et al.* Metabolite-initiated protein misfolding may trigger Alzheimer's disease. *Proc. Natl Acad. Sci. USA* **101**, 4752–4757 (2004)
FURTHER READING Barnham, K. J., Masters, C. L. & Bush, A. I. Neurodegenerative diseases and oxidative stress. *Nature Rev. Drug Discov.* **3**, 205–214 (2004)