HYPOLIPIDAEMIC DRUGS

Antagonizing the bile-acid receptor

For centuries, the gum resin of the tree *Commiphora mukul* (guggulu in sanskrit) has been used in Ayurvedic medicine to treat obesity and lipid disorders, and since 1997, the resin extract — gugulipid — has been approved to treat hyperlipidaemia in India. Guggulsterone, one of the compounds that is present in gugulipid, reduces cholesterol levels. In *Science*, Moore and colleagues show that the molecular mechanism by which cholesterol is lowered is through antagonism of the farnesoid X receptor (FXR).

Cholesterol is tightly regulated at many levels. One way that cholesterol is released is in the form of bile acids. When these acids are high, a negative-feedback loop is activated to reduce cholesterol production by the liver. This negative regulation is mediated by the bile-acid nuclear-hormone receptor FXR. As FXR can be activated by compounds that are structurally unrelated to bile acids, and guggulsterone decreases hepatic cholesterol levels in rodent models, the authors proposed that this plant product could act by modulating FXR activity.

The effect of guggulsterone on FXR activity was tested using transient transfections with a synthetic FXR-responsive reporter plasmid. The compound strongly inhibited FXR activation by the most potent of the bile-acid agonists — chenodeoxycholic acid (CDCA) — in a dose-dependent manner. Similar results were seen with the promoter of the orphan receptor SHP (short heterodimer partner), which contains an FXR/retinoid X receptor heterodimer-binding site and is induced by bile acids. To test whether guggulsterone directly antagonizes FXR, a fluorescence resonance energy transfer (FRET) assay was used. In the presence of the agonist CDCA, a peptide that contained the receptor-binding domain of the steroid-receptor coactivator-1 is specifically recruited to the FXR ligand-binding domain. In an elegant demonstration, FRET analysis revealed that CDCA and guggulsterone directly compete for the ligand-binding domain. Guggulsterone did not activate or inhibit transactivation by several other receptors that are associated with lipid metabolism. Finally, the authors showed that it is the FXR antagonistic activity of guggulsterone that is required for its hypolipidaemic effects. The cholesterol-lowering effect of the drug was absent in Fxr-deficient mice. Interestingly, Fxr-deficient mice do not have decreased cholesterol levels, which could possibly be due to chronic compensatory pathways.

Although a standardized preparation of gugulipid has never been compared directly with other hypolipidaemic drugs, such as statins, gugulipid seems to have comparable efficacy and fewer side effects. Its mechanism of action is different from that of the statins, so it is likely that gugulipid would be useful in combination with them, or in individuals who have problems tolerating statins. However, the effect on FXR that was described in the paper suggests that guggulsterone might induce drug metabolism and thereby decrease the effectiveness of other drugs. This work has implications for other relatively promiscuous nuclear-hormone receptors that might mediate the biological effects of different natural products. Further characterization of these effects could identify agents with desirable therapeutic activities.

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References and links

ORIGINAL RESEARCH PAPER Urizar, N. L. *et al.* A natural product that lowers cholesterol as an antagonist ligand for the FXR. *Science* 2002 May 2 (doi: 10.1126/science.1072891)

WEB SITES Moore's laboratory: http://public.bcm.tmc.edu/mcb/faculty/moore_d.html

IN BRIEF

CARDIOVASCULAR DISEASES

First experience with direct factor Xa inhibition in patients with stable coronary disease. A pharmacokinetic and pharmacodynamic evaluation

Dyke, C. K. *et al. Circulation* 2002 Apr 29 (doi: 10.1161/01.CIR.0000016351.12759.52)

Inhibition of factor Xa — which has a key role in the formation of blood clots — might be more effective and safer than current treatments, such as heparin and warfarin, for preventing the formation of potentially life-threatening blood clots in patients with coronary artery disease. In this Phase Ib trial involving 73 patients, the small-molecule factor Xa inhibitor DX-9065a (Daiichi Pharmaceutical Company) was shown to be safe in patients with stable coronary disease who were receiving standard therapy (for example, aspirin, beta-blockers and statins), paving the way for larger clinical studies with this new drug class.

COMPUTATIONAL CHEMISTRY

A virtual screening method for prediction of the hERG potassium channel liability of compound libraries

Roche, O. *et al. ChemBioChem* **3**, 455–459 (2002)

Compounds that block the hERG potassium channel cause QT prolongation, a disorder of cardiac-action-potential repolarization that can lead to potentially lethal cardiac arrhythmias. More than 70 common drugs have been shown to have this serious side effect. Using various techniques to find appropriate molecular descriptors, Roche *et al.* developed a virtual-screening method for predicting hERG affinity, which could classify known blockers and non-blockers with 71% and 93% accuracy, respectively.

BLOOD DISEASES

Treatment of hypereosinophilic syndrome with imatinib mesilate

Gleich, G. J. *et al. Lancet* **359**, 1577–1578 (2002)

Hypereosinophilic syndrome (HES) is a potentially fatal blood disease that is characterized by an increase in inflammatory white blood cells, which results in organ damage. Drugs used in patients with chronic myelogenous leukemia (CML) have been used in HES, but with limited effect. Gleich *et al.* tested Gleevec (imatinib mesilate), the recently approved breakthrough treatment for CML, in five patients with HES, and four showed marked improvements; however, the underlying mechanism remains to be elucidated.

GENOMICS

Complete genome sequence of the model actinomycete *Streptomyces coelicolor* A3(2)

Bentley, S. D. *et al. Nature* **417**, 141–147 (2002)

Actinomycetes, such as *Streptomyces coelicolor*, produce two-thirds of the natural antibiotics in use, and also many anticancer agents. The genome sequence of *S. coelicolor*, the model actinomycete, should facilitate experiments aimed at manipulating the biosynthetic gene clusters of therapeutic natural products to produce novel agents with potentially improved activities.