Structure of CETP identified

Researchers have confirmed the structure of cholesteryl ester transfer protein (CETP), in a recent paper published in *Nature Structural and Molecular Biology*.[1]

CETP is a glycoprotein that plays an important role in the metabolism and remodelling of HDL. In particular, CETP facilitates heteroexchange, resulting in the net movement of cholesteryl ester from atheroprotective HDL particles to atherogenic triglyceride-rich lipoproteins, such as very-low density lipoprotein (VLDL) and, at the same time, transport of triglycerides from VLDL to HDL. This process has been implicated in reverse cholesterol transport, in which excess cholesterol is removed from peripheral tissues and returned to the liver for elimination. While studies suggest links between CETP, HDL cholesterol levels and cardiovascular disease, CETP function and structure have yet to be fully elucidated.

The researchers used crystallography and diffraction data to determine the structure of CETP, derived from a host in vitro cell line (dihyrofolate reductase-deficient Chinese hamster ovary cell line DG44).

CETP was shown to have a 'boomerang' shape with a tunnel 60 Å long traversing the core of the protein. This tunnel can accommodate two cholesteryl esters and is plugged by a phospholipid molecule at each end. The two tunnel openings are large enough to allow lipid access, aided by a helix forming a flexible lid, and a mobile flap that opens to allow a wider opening, thereby facilitating passage of lipids. The curvature of the concave surface of CETP makes it well suited to interaction with HDL although conformational changes are required when CETP binds larger particles, such as VLDL.

The structure reported for CETP provides a basis for future study of this protein.

Reference

1. Qiu X, Mistry A, Ammirati MJ et al. Crystal structure of cholesteryl ester transfer protein reveals a long tunnel and four bound lipid molecules. Nature Structural & Molecular Biology 2007;14;106-13.

Commentary

There is a huge current interest in CETP and the potential of its inhibition as a strategy for treating atherosclerosis. This issue is currently under a cloud following the adverse effects of the CETP inhibitor, torcetrapib, in the recently terminated ILLUMINATE trial. What is uncertain is whether the problem with torcetrapib was due to problems with inhibiting CETP or to problems unique to the torcetrapib molecule. If the latter explanation is true, then inhibition of CETP as a therapeutic strategy remains viable and the search for new inhibitors without adverse effects will be a high priority. The elucidation of the structure of CETP will greatly advance such endeavours. The fact that CETP is an extremely hydrophobic molecule (almost completely insoluble in water) made it extremely difficult to crystallize and highlights the magnitude of what Dr Qiu and his colleagues have achieved.