

prokaryotes and eukaryotes⁸, has four domains — two transmembrane domains and two cytoplasmic ATP-binding cassettes, which provide the energy for ligand transfer. The ABC transporters carry diverse ligands, including ions, amino acids, sugars, cytotoxic and anti-malarial drugs, phospholipids, sterols, vitamins, iron chelates and proteins. In the newly discovered CERP protein, the two halves of the molecule are linked by a long, charged, hydrophobic segment. A low-resolution structure of a typical ABC transporter, the multidrug-resistance P-glycoprotein, reveals a large aqueous chamber in the membrane, the walls of which are created by the transmembrane domains. This chamber has a large pore, which is open to the outside of the cell, as well as an opening into the lipid phase of the membrane (but not into the cytoplasm on the other side)⁹. Ligand might be transferred from the lipid phase to the aqueous chamber, then to an acceptor on the outside of the cell. Other, auxiliary proteins may be required to help transport bulky substrates.

The CERP transporter is probably made

in the cytoplasm of peripheral cells (Fig. 1) and then transferred to cholesterol rafts in the plasma membrane. Here, cholesterol increases the thickness of the lipid bilayers^{2-4,10}, favouring the segregation of proteins with long transmembrane domains to this location in the cell. The CERP probably transfers free cholesterol and phospholipid between the inner and outer leaflets of the plasma membrane. At the outer side, the cholesterol is then captured by apoAI for the production of HDL. However, we do not yet know the precise localization of CERP in the cell, or whether free cholesterol and phospholipid are its true ligands. The CERP transporter could transfer other ligands, such as a protein that facilitates the transfer of sterols and lipid.

Not all patients with Tangier disease have coronary heart disease, and Schmitz's group suggest³ that certain variants of the *CERP* gene may predispose to atherosclerosis by targeting cholesterol-packed macrophages to the artery. But based on the distribution of mutations in people with Tangier disease and familial HDL deficiency, there is no

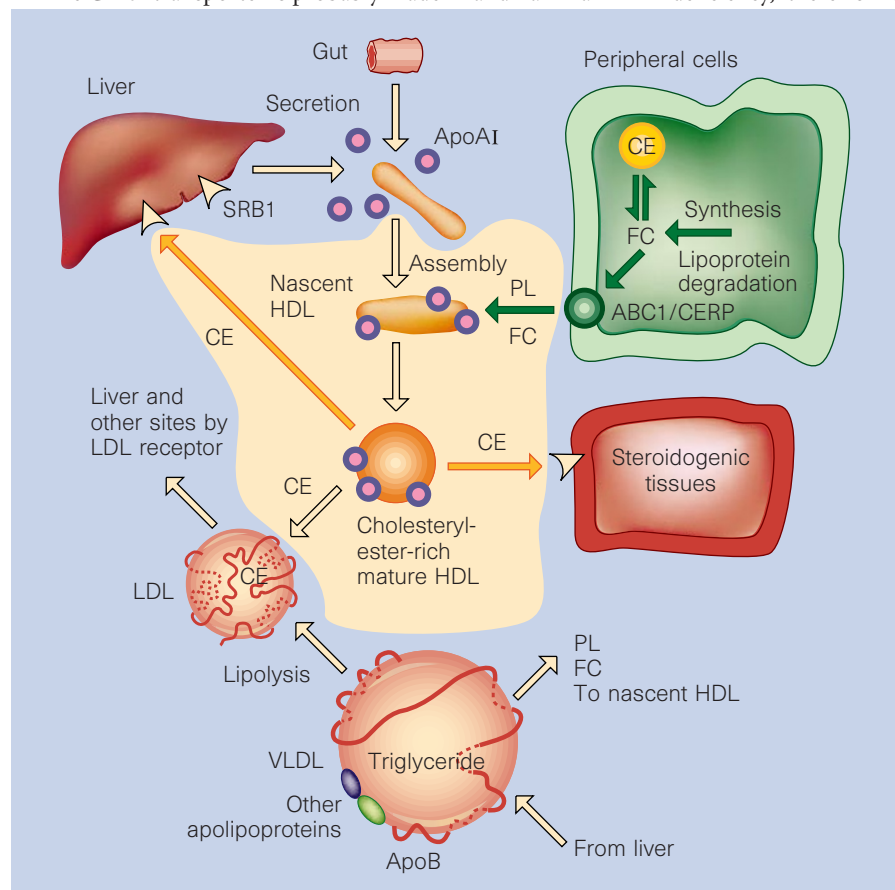


Figure 1 Cholesterol and Tangier disease. The newly discovered²⁻⁴ cholesterol-efflux regulatory protein (CERP) is necessary for the bulk transfer of free cholesterol (FC) and phospholipid (PL) out of cells. In the extracellular fluid, apolipoprotein-AI (apoAI) and nascent high-density lipoprotein (HDL) act as acceptors for the cholesterol. The free cholesterol in mature HDL is esterified (cholesteryl ester, CE) and transferred to low-density lipoprotein (LDL) and to cells by scavenger receptor B1 (SRB1). ApoB is the main apolipoprotein in LDL and very low-density lipoprotein (VLDL). So, in normal cells, ApoAI is recycled. In patients with Tangier disease, however, the absence of free cholesterol and phospholipid aborts the formation of HDL owing to defects in CERP. The apoAI is rapidly cleared from the circulation and degraded. Events that are defective in Tangier disease are shaded (light).



100 YEARS AGO

A few years ago a station was established near the town of San Marcos, Texas ... As the rainfall in western Texas is untrustworthy, the Commission determined to bore an artesian well to supply the water for its new station. ... Soon after the San Marcos well was opened a number of living animals began coming up with the water. So far, four kinds of Crustacea and a salamander have been seen, and of these quite a number have been obtained. The Crustacea are new to science and were described by Dr. James E. Benedict, of the Smithsonian Institution. They are white and perfectly blind. Most of the shrimps and crab-like animals have eyes set on the extremities of stalks that project above the surface. The shrimps from this well have the stalks, but the eyes have disappeared.

It is announced that Sir Edmund Antrobus is desirous of selling Stonehenge, the famous and mysterious monument on Salisbury Plain. Thinking it right that the nation should have the opportunity of purchasing this great relic of antiquity, the owner has offered it to the Government, with about 1300 acres of surrounding land (subject to certain pasturage and sporting rights), for the sum of 125,000*l*.

From *Nature* 24 August 1899.

50 YEARS AGO

Goethe, the greatest poet that Germany has produced, was a dominating intelligence who must claim a prominent place in any history of the human mind, and he devoted a considerable part of his effort to scientific studies. ... Yet we must face the fact that while there is in this scientific work of his much that is of the greatest interest, for the light that it throws on a superlative and complex character, there is not much — except, some would contend, in his botanical studies — that is important for the history of science. ... Goethe's scientific work may, perhaps, almost stand with Newton's work on theology and chronology — excellent, in many ways, if judged by the standard of the times, very important in the eyes of its producer, but not likely to have been remembered today had it been produced by a lesser man.

From *Nature* 27 August 1949.