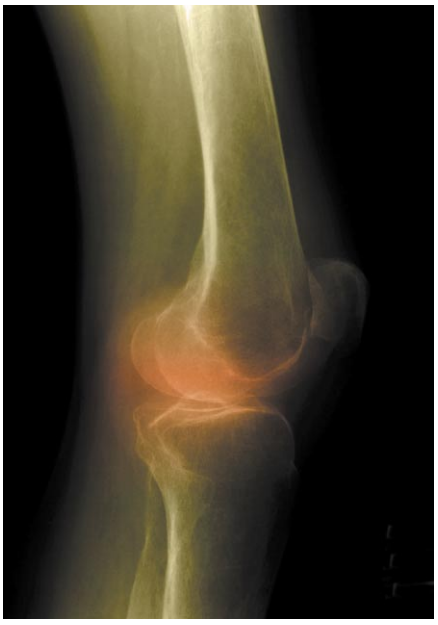
patients with SLE was fully functional and able to stimulate B cell activation *in vitro*. Raised BLyS was associated with a higher level of anti-dsDNA antibodies (a marker for SLE) but no increase in disease activity or damage. BLyS, the authors conclude, could therefore be a useful marker for autoimmune activation and probably also plays a crucial role in triggering activation of dsDNA-driven autoimmune B cells in people with SLE (Ref. 3).

A similar study measured BLyS levels in 22 patients with a variety of immune-based rheumatological disorders[2]. Cheema and coworkers found elevated BLyS levels in 15 patients and that these levels correlated with serum immunoglobulin levels.

Compromising immunity

Anti-BLyS antibodies will probably be administered as an intravenous or subcutaneous injection and could provide a therapy that patients self-administer once or twice a month. However, there is a chance that lowering BLyS levels could diminish B cell activity to such an



extent that patients become immunocompromised. However, Stump says, 'The BLyS receptor is not seen on early B-cell precursors. Therefore, if treatment is monitored carefully, this potential problem should be manageable by, for example, intermittent treatment to enable the stock of B cells to be restored.' Kimberly adds: 'Initial defence against viral infection is phagocyte-, NK cell- and T cell-mediated and so should not be impaired by these antibodies. Furthermore, endogenous antibody against tumours is not usually the first line of defence.' Kimberly concludes: 'In conditions where there is abnormally high B-cell activity (with antibody production), one can anticipate that reducing BLyS will be beneficial. However, as "normal" levels of BLyS seem very low, it is not yet clear what is required to maintain normal immune activity.'

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Targeting 'good' cholesterol to treat heart disease

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Current clinical strategies to manage blood cholesterol levels are confined solely to reducing the level of low-density lipoproteins (LDLs, or 'bad' cholesterol). However, scientists from CV Therapeutics (CVT, Palo Alto, CA, USA) have recently reported further advances on a mechanism to raise high-density lipoprotein (HDL, or 'good' cholesterol) levels[1]. Raising HDL levels offers an entirely new treatment solution for cholesterol management that could have a substantial impact on the prevention and treatment of cardiovascular (CV) disease.

Blood cholesterol and heart disease

CV disease is the largest single killer in the Western world. A high blood cholesterol level is a strong risk factor in CV disease because cholesterol can deposit on blood vessel walls, promoting the growth of fatty (atherosclerotic) plaques. These plaques obstruct blood flow and usually promote blood clotting, potentially resulting in, for example, myocardial infarction, stroke and peripheral vascular disease.

Cholesterol is transported in a soluble form in the blood as lipoproteins. LDLs deliver cholesterol to body cells that need it and high plasma LDL concentrations are associated with a high

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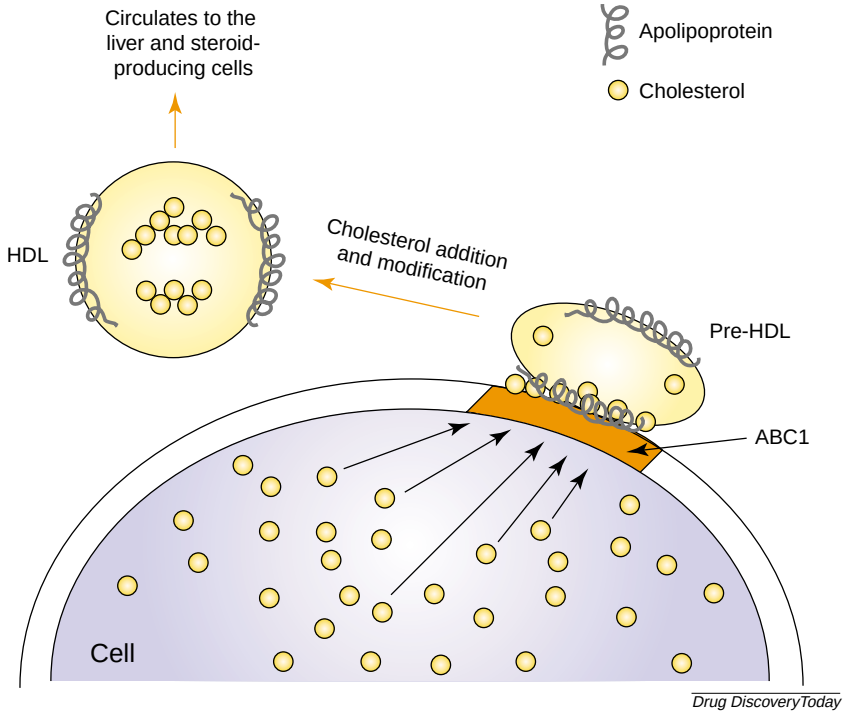

Figure 1. The ABC1 protein pumps cholesterol out of cells, where it can be converted to HDL.

incidence of CV. By contrast, HDLs remove excess cholesterol from cells and transport it to the liver for elimination; consequently, high HDL levels are associated with a decreased risk of heart disease.

The ABC1 discovery

Richard Lawn, Vice-President of Discovery Research at CVT explains: 'In trying to elucidate a mechanism to modulate HDL levels, we investigated Tangier disease (TD), a rare genetic disorder that is characterized by extremely low plasma HDL levels and a biochemical defect in the cellular efflux of cholesterol to HDLs. Such patients have a 5–6-fold increased CV risk compared with matched controls.'

ABC1 (ATP-binding cassette transporter, a member of the ATP-binding cassette family) was identified as the defective gene in TD using a combined strategy of gene expression microarray analysis, genetic mapping and biochemical studies[2]. Tissue culture experiments showed that increasing ABC1 protein production enhanced cholesterol removal from the cells[2]. Thus, ABC1 has the properties of a key protein in the cellular lipid removal pathway (Fig. 1), as emphasized by the consequences of its defect in patients with TD. Other studies[3], using *ABC1* knockout mice, showed that mice with no copies of the gene had no circulating HDL, whereas heterozygous mice had about half the normal HDL levels.

Regulatory mechanisms for ABC1

The next step was to discover the regulatory mechanism that controls the production of ABC1 protein. Constructs containing sequential deletion mutations of 1.75 kb of the *ABC1* 5′-flanking region were prepared and fused to a luciferase reporter gene[1]. Cultured macrophages (often found in the core of atherosclerotic plaques, where they are full of cholesterol) were then transfected with the constructs and gene expression activity measured. This identified the *ABC1* promoter region – a stretch of DNA vital for the control of gene transcription.

Cloning techniques identified two separate units, the LXR and RXR proteins, which together function as nuclear hormone receptors[1]. As such, when an appropriate ligand binds to the LXR–RXR dimer, the resulting complex attaches to, and turns on, transcription of the *ABC1* gene.

The scientists then identified ligands that bind to the LXR–RXR dimer[1]. The LXR–RXR ligands, 9-*cis* retinoic acid and 20(*S*) hydroxycholesterol, increased gene transcription 8–10-fold when used alone, or 80-fold when used together, in cultured macrophage cells. The ligands also enabled the cells to efflux cholesterol, even though normally they cannot do this unless *ABC1* expression is induced using cAMP analogues.

The next step

Lynn Smaha, immediate past-President of the American Heart Association and Executive Vice-President, Guthrie Clinic (Sayre, PA, USA) commented that: 'The identification of the ligand that is related to the body's own ability to produce HDL is an important finding. This approach could enable the body's own processes to raise HDL, which is potentially a better option than other approaches currently under study, such as the injection of foreign substances (e.g. genetically engineered particles) that are intended to act like HDL.'

Lawn reports that having now identified the intracellular signals that increase *ABC1* activity, the company is actively searching for other, more potent ligands of LXR–RXR, using the promoter element to screen a wide range of potential compounds.

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