DOI:

10.1038/nri2087

T CELLS

LIGHTing up lipid metabolism

Atherosclerosis is characterized by the dysregulation of lipid metabolism (dyslipidaemia), in combination with inflammation. Recent studies have linked members of the tumour-necrosis factor (TNF) superfamily to the development of atherosclerosis, but the exact mechanism is unknown. New research, published in *Science*, now shows that signalling through lymphotoxin- β receptor (LT β R) by members of the TNF superfamily contributes directly to lipid metabolism.

Lymphotoxin (LT) and LIGHT, which are members of the TNF superfamily and are primarily expressed by T cells, have both been shown to bind to LT β R. Using transgenic mice that overexpress LIGHT in the T-cell lineage, the authors showed that T-cell-derived LIGHT promotes dyslipidaemia. These mice

expressed higher levels of cholesterol and triglycerides in the blood. In addition, the transfer of T cells from LIGHT-transgenic mice to wild-type mice resulted in elevated plasma cholesterol concentrations in the wild-type mice.

To further examine the role of LIGHT in mediating dyslipidaemia, the LIGHT-transgenic mice were crossed with *Ltbr*^{-/-} mice. The level of cholesterol and triglycerides in the blood of these mice was similar to wild-type mice, indicating that LT β R-mediated signalling is required for LIGHT-dependent dyslipidaemia.

Because of the association of lipid metabolism with the liver, the authors next examined hepatic gene expression profiles in the LIGHT-transgenic mice. In these mice, the expression level of hepatic lipase, a key enzyme

in lipid metabolism, was only 5–10% of that of wild-type mice. Further studies indicated that the direct interaction of LIGHT on T cells with LT β R on hepatocytes inhibited the expression of hepatic lipase.

Administration of an LT β R-immunoglobulin fusion protein, which acts as a soluble decoy protein and blocks both LT- and LIGHT-induced signalling, increased the expression of hepatic lipase and reversed dyslipidaemia in a mouse model of atherosclerosis.

So, the data indicate that T cells in the liver, through the expression of LT β R ligands, have an important role in regulating hepatic-mediated lipoprotein homeostasis, and that agents that block the activation of LT β R might have therapeutic potential in the treatment of dyslipidaemia and atherosclerosis.

Olive Leavy

ORIGINAL RESEARCH PAPER Lo, J. C. *et al.*
Lymphotoxin β receptor-dependent control of
lipid homeostasis. *Science* **316**, 285–288 (2007)