G PROTEIN-COUPLED RECEPTORS

Case builds for TGR5 as metabolic syndrome target

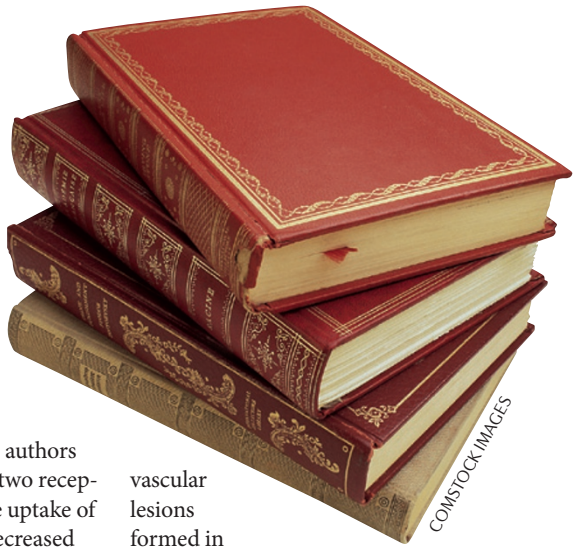
Activation of TGR5, a G protein-coupled receptor for bile acids, has been linked to both improved glycaemic control and enhanced energy expenditure. Now, the discovery by Pols and colleagues, reported in *Cell Metabolism*, that activation of TGR5 also protects against the development of atherosclerosis could provide a further boost to its appeal as a potential therapeutic target for metabolic syndrome.

The team behind the study previously showed that activation of TGR5 by bile acids protects mice from obesity and insulin resistance. In the current paper, they set out to investigate the potential involvement of bile acids and TGR5 in inflammation, which contributes to the progression of atherosclerosis, an important facet of metabolic syndrome.

Pols *et al.* initially established the presence of functional, agonist-responsive TGR5 in primary macrophages and macrophage cell lines. They then showed that its activation inhibited the production of inflammatory cytokines — such as tumour necrosis factor (TNF) and interleukins — in these cells by comparing the response to lipopolysaccharide of primary macrophages from $Tgr5^{+/+}$ mice and $Tgr5^{-/-}$ mice in the presence and absence of INT-777, a TGR5-specific semisynthetic bile acid. Further analysis revealed that TGR5 overexpression or activation using INT-777 induced cyclic AMP signalling and thereby inhibited the transcriptional activity of nuclear factor κB (NF-κB), consequently suppressing the production of cytokines in macrophages.

As well as contributing to inflammation through the production of cytokines, however, macrophages can also scavenge oxidized low-density lipoproteins (LDLs) in the blood vessel wall to form foam cells, which — when they accumulate — can initiate the formation of an atherosclerotic plaque. The authors observed reduced levels of two receptors that are involved in the uptake of modified LDL, as well as decreased LDL loading, in INT-777-stimulated macrophages from $Tgr5^{+/+}$ mice but increased levels of these receptors in macrophages from $Tgr5^{-/-}$ mice, indicating that TGR5 also inhibits the formation of macrophage foam cells.

Given these observations, the authors wondered whether TGR5 activation could attenuate the development of atherosclerosis, so they cross-bred $Tgr5^{-/-}$ or $Tgr5^{+/+}$ mice with mice deficient in the LDL receptor ($Ldlr^{-/-}$ mice), which are susceptible to atherosclerosis, and added INT-777 to the atherogenic diet of the $Ldlr^{-/-}Tgr5^{-/-}$ and $Ldlr^{-/-}Tgr5^{+/+}$ cohorts. Significantly fewer vascular lesions were formed in the aortic root of INT-777-treated $Ldlr^{-/-}Tgr5^{+/+}$ mice but not $Ldlr^{-/-}Tgr5^{-/-}$ mice, and the atherosclerotic plaques from these lesions contained fewer macrophages as well as lower levels of TNF and interleukin-1 transcripts. Finally, the authors confirmed that leukocytes were responsible for the TGR5-mediated inhibition of atherosclerosis by showing that fewer vascular lesions formed in response to INT-777 treatment in $Ldlr^{-/-}$ mice transplanted with the bone marrow of $Tgr5^{+/+}$ mice, compared with $Ldlr^{-/-}$ mice transplanted with the bone marrow of $Tgr5^{-/-}$ mice.



COMSTOCK IMAGES

So, the activation of TGR5 by INT-777 decreased pro-inflammatory cytokine production by cyclic AMP-mediated inhibition of NF-κB signalling, and reduced oxidized LDL uptake in macrophages to confer protection from atherosclerosis. Given the interest in drug development around TGR5 prior to this report, an array of selective and potent TGR5 agonists are available, including synthetic and natural compounds (such as oleanolic, ursolic and betulinic acid), and the opportunities for such compounds as potential treatments for metabolic syndrome might be substantial.

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ORIGINAL RESEARCH PAPER Pols, T. W. H. *et al.* TGR5 activation inhibits atherosclerosis by reducing macrophage inflammation and lipid loading. *Cell Metab.* **14**, 747–757 (2011)