T CELLS

Endogenous agonists for orphan RORγ

Expression of retinoic acid receptor-related orphan receptor-γ (RORγ) is induced during the differentiation of T helper 17 (T_H17) cells and is required for their production of cytokines such as interleukin-17 (IL-17) and IL-22. Until now, a high-affinity ligand for RORγ in T_H17 cells had not been identified. Reporting in *Nature Chemical Biology*, Hu *et al.* show that the cholesterol precursor desmosterol is a potent endogenous agonist for RORγ and is essential for the generation of T_H17 cells.

Sterols are needed in proliferating cells as components of cell membranes and as signalling molecules for nuclear and cell-surface receptors, and their levels are controlled by a balance of synthesis, uptake, metabolism and efflux. Consistent with this requirement for sterols in activated T cells, Hu *et al.* show that the expression of most genes involved in cholesterol biosynthesis and uptake is increased, whereas the expression of genes involved in cholesterol metabolism (especially oxysterol formation) and efflux is decreased, in activated T cells cultured under T_H17 cell-polarizing conditions, as well as during the *in vitro* differentiation of T_H1 cells and regulatory T (T_{Reg}) cells. Moreover, the use of inhibitors (such as ketoconazole) that block an enzyme involved in cholesterol synthesis selectively decreased T_H17 cell differentiation without affecting the expression of RORγ.

As blocking of cholesterol synthesis selectively decreased the transcription of RORγ target genes, the authors next investigated whether cholesterol precursors could function as ligands for RORγ. Among those tested, desmosterol and zymosterol potently increased co-activator recruitment by RORγ and were able to outcompete binding by RORγ antagonists. Desmosterol and zymosterol also promoted RORγ transcriptional activity in a reporter assay. Finally, the addition of these sterols to T_H17 cell-polarizing cultures overcame the effects of cholesterol synthesis blockade by ketoconazole, and increased IL-17 production and T_H17 cell differentiation in an RORγ-dependent manner. Notably, desmosterol did not increase the differentiation of T_H1 cells or T_{Reg} cells.

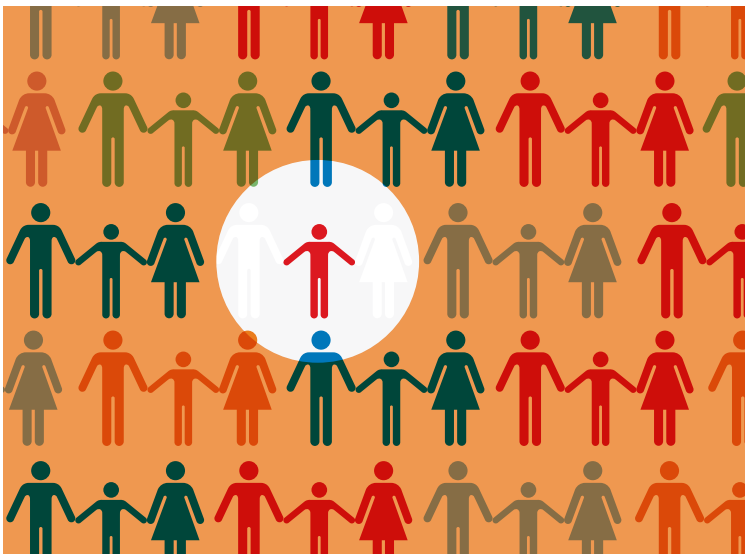
> “desmosterol is the main endogenous agonist for RORγ in T_H17 cells”

The findings that desmosterol and cholesterol were the only sterols that accumulated at detectable levels in T_H17 cells, and that ketoconazole treatment markedly reduced desmosterol but not cholesterol levels, confirmed that desmosterol is the main endogenous agonist for RORγ in T_H17 cells.

Further analysis of sterol derivatives revealed that sulphated sterols are also potent agonists of RORγ, with desmosterol sulphate being a stronger agonist than desmosterol. Interestingly, a metabolic shift in T_H17 cells favours the formation of sulphated sterols and the authors suggest that this promotes activation of RORγ rather than activation of the LXR oxysterol receptors, which increase cholesterol efflux and inhibit T_H17 cell differentiation.

Finally, the authors show that IL-17 production by γδ T cells also depends on cholesterol synthesis, such that treatment of mice with ketoconazole could inhibit psoriasis-like disease driven by IL-17-producing γδ T cells.

Lucy Bird



S.Bradbrook/NPG

ORIGINAL RESEARCH PAPER Hu, X. *et al.* Sterol metabolism controls T_H17 differentiation by generating endogenous RORγ agonists. *Nature Chem. Biol.* http://dx.doi.org/10.1038/nchembio.1714 (2015)

FURTHER READING Tall, A. R. & Yvan-Charvet, L. Cholesterol, inflammation and innate immunity. *Nature Rev. Immunol.* **15**, 104–116 (2015)