IMMUNOLOGICAL DISORDERS

Spotting the troublemakers

> a method for identifying potentially pathogenic T_H17 cells in humans

T helper 17 (T_H17) cells produce interleukin-17 (IL-17) and are thought to promote various inflammatory conditions, including Crohn's disease. However, not all T_H17 cells are pathogenic, and some have beneficial immunoregulatory functions. As such, there is interest in developing therapeutics that specifically target disease-promoting T_H17 cells. A recent study by Ramesh *et al.* now describes a method for distinguishing pathogenic from non-pathogenic T_H17 cells in humans.

Recent studies in mice have shown that pathogenic T_H17 cells produce interferon-γ (IFNγ) and express high levels of the IL-23 receptor (IL-23R). Previous work has also suggested that human memory T_H17 cells can be divided into two main subsets on the basis of chemokine receptor expression — $CCR6^+CCR4^{hi}$ T_H17 cells express IL-17, but not IFNγ, whereas $CCR6^+CXCR3^{hi}$ T_H17 cells express both IL-17 and IFNγ. Consistent with this, Ramesh *et al.* identified similar T_H17 cell populations in blood from healthy adults. Compared with $CCR6^+CCR4^{hi}$ T_H17 cells, $CCR6^+CXCR3^{hi}$ T_H17 cells produced lower levels of IL-17 but expressed higher levels of mRNAs encoding IL-23R and other pro-inflammatory mediators, such as CC-chemokine ligand 3 (CCL3), CCL4, CCL5 and granzyme B. By contrast, $CCR6^+CCR4^{hi}$ T_H17 cells expressed higher levels of mRNAs encoding anti-inflammatory mediators, such as IL-10 and the IL-1R antagonist protein. However, despite these differences in IL-23R expression, both populations showed a similar, weak response to IL-23-mediated stimulation *in vitro*. The authors therefore hypothesized that potentially pathogenic IL-23-responsive T_H17 cells represent only a minor subset of the $CCR6^+CXCR3^{hi}$ T cell population.

In agreement with this, they were able to identify a subpopulation of $CCR6^+CXCR3^{hi}$ T cells that was enriched for pathogenic characteristics, including enhanced responsiveness to IL-23, as determined by increased phosphorylation of signal transducer and activator of transcription 3 (STAT3) and increased production of IL-17. These cells specifically expressed multidrug resistance protein 1 (MDR1; also known as P-glycoprotein), which is a membrane transporter that can promote the efflux of a broad range of substrates. Notably, the authors found that $MDR1^+$ memory T cells were enriched in biopsy samples from the inflamed gut of patients with Crohn's disease compared with either peripheral blood from the patients or biopsy samples from non-inflamed gut. Furthermore, $MDR1^+$ T cells from inflamed gut tissue expressed genes associated with pathogenic T_H17 cell activity, whereas $MDR1^-$ T cells from the same biopsy samples expressed genes associated with non-pathogenic T_H17 cells.

Finally, in *ex vivo* culture experiments, the authors showed that $MDR1^+$ T_H17 cells from healthy humans are resistant to the immunosuppressive effects of glucocorticoids. Strikingly, treatment with glucocorticoids actually led to the enrichment of $MDR1^+$ T_H17 cells within mixed T cell cultures. Notably, patients with Crohn's disease often develop steroid-resistant disease, but the reasons for this have not been clear.

Taken together, these findings have important clinical implications as they not only describe a method for identifying potentially pathogenic T_H17 cells in humans but also suggest a possible mechanism for why certain patients with Crohn's disease do not respond to glucocorticoid therapy.

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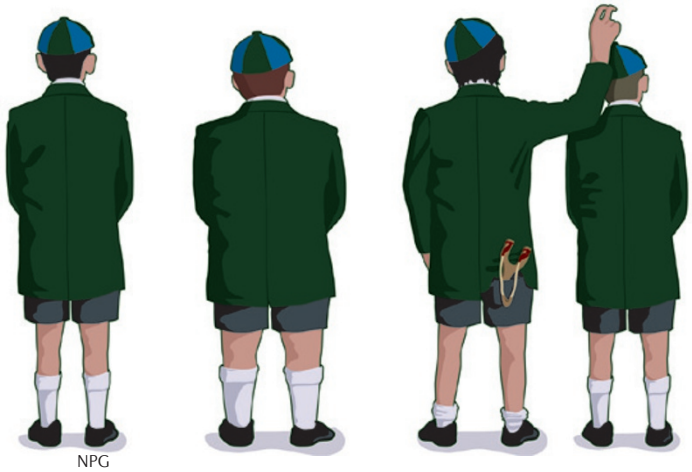
ORIGINAL RESEARCH PAPER Ramesh, R. *et al.* Pro-inflammatory human Th17 cells selectively express P-glycoprotein and are refractory to glucocorticoids. *J. Exp. Med.* **211**, 89–104 (2014)



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