

Immunology News: A New Type of T Cell Is Discovered

Immunology is a young, fast-moving, discipline. Today's dogma is often disproved tomorrow. But most people would have thought that the fundamental division of helper cells into 'Th1' and 'Th2' was conclusive. Not so, it turns out.

The Dogma

T helper (Th) cells are an important part of the adaptive immune system. They express T cell receptors (TCRs) that recognise a specific protein bound to class II MHC molecules and activation causes cytokine release. They are important in the defence against microbes but also induce inflammation in immune-mediated diseases. In the 1980s, Mosmann showed that CD4+ T lymphocytes could be divided into 'Th1' and 'Th2'.¹

- The cytokine interleukin-12 (IL-12) promotes the development of Th1 cells, which secrete IFN- γ , IL-2 and TNF- β (lymphotoxin); these drive cell-mediated immunity to eliminate intracellular pathogens.

- In contrast, T cells stimulated in the presence of IL-4 turn into Th2 cells which secrete more IL-4, IL-5, IL-10 and IL-13, and up-regulate antibody-mediated responses for elimination of extracellular pathogens.

Recently, regulatory T cells (Tregs) have been described which are thought to inhibit unwanted immune responses to self antigens. When this regulation fails, autoimmune disease results. Multiple sclerosis was thought to be a classic example of a disease driven by Th1 cells, whereas allergy was due to excessive Th2 cytokine production.

A major plank of evidence for all of this came from Experimental Autoimmune Encephalomyelitis (EAE). For instance, studies with IL-12 knock out mice (IL-12^{-/-}),² or using IL-12p40 neutralising antibodies,^{2,3} have shown that IL-12 is necessary for disease expression; hence Th1 cells and IFN- γ drive EAE. All very tidy.

The problem

According to all of this, mice which lack certain critical components of the Th1-IFN- γ pathway (IFN- γ ^{-/-}, IFN-R^{-/-}, IL-12R β ^{-/-}, and IL-12p35^{-/-} mice) should not get EAE. Unfortunately however, they do.

The solution

The first step in sorting all this out was the finding that the subunit p40 is shared by both IL-12 and a newly-discovered cytokine called IL-23.⁸ IL-23 is secreted by activated dendritic cells and stimulates IFN- γ production and proliferation of blast T cells and memory T cells.⁸ Becher et al⁷ showed conclusively that mice deficient in the specific p35 subunit of IL-12 (p35^{-/-}) develop severe EAE whereas those deficient to the common p40 subunit (p40^{-/-}) were resistant to EAE. So IL-12 is not responsible for EAE.

Daniel Cua, from Schering-Plough Biopharma, reasoned that all the p40 knock-out experiments were flawed and that deficits attributable to IL-12 deficiency may have actually been due to lack of IL-23. His team proved this by manipulating mice cells *in vitro* and seeing if they induced EAE on transfer to naïve mice. The result was clear: T cells cultured *in vitro* with IL-23, but not IL-12, caused severe clinical signs of EAE on transfer (Figure 1).⁹ In IL-23 deficient mice, Th1 cells invaded the CNS, but did not cause disease. So IL-12 and Th1 cells do not drive EAE! This is a major paradigm shift....

What sort of T cells does IL-23 induce?

CD4+ T cells from IL-23p19^{-/-} knockout mice are

specifically unable to produce IL-17.¹⁰ So the thinking is that IL-23 induces a new brand of helper T cells called 'Th17' cells characterised by their production of IL-17. IL-17 has not had much of a press until now. It induces the secretion of pro-inflammatory cytokines tumour necrosis factor (TNF), IL-1 and IL-6 from macrophages.¹¹ IL-17 also induces production of IL-6, IL-8, prostaglandin E₂ and granulocyte colony-stimulating factor (G-CSF) from rheumatoid synovial fibroblasts and IL-6 from a variety of stromal cells.¹² Anti-IL-17 treatment of wild type mice immunised with myelin protein PLP are partially protected against EAE.⁹

How do Th17 cells develop?

As well as IL-23, TGF- β 1 is important in the development of Th17 cells. Mice over-expressing TGF- β 1 had increased numbers of Th17 cells and worse autoimmune disease.¹³ Th17 differentiation is inhibited by the products of Th1 and Th2 cells, IFN- γ and IL-4 respectively.¹⁴ Development of Th17 cells is promoted by the combination of transforming growth factor (TGF- β 1) and IL-6.^{13,15} These cytokines are produced by many cells. TGF- β 1 alone induces the differentiation certain subsets of Treg cells.¹⁶ When TGF- β 1 is combined with IL-6 it inhibits the expression of FoxP3, a gene transcription factor essential for Treg development, thus promoting Th17 and suppressing Treg cell development.^{13,15} In the steady state TGF- β 1 will induce FoxP3+ Tregs and maintain self-tolerance. When there is infection or inflammation, IL-6 produced by the innate immune system will suppress Tregs cells and induce pro-inflammatory response by Th17. So now, a scheme like this can be drawn (Figure 2).

Th17 cells drive autoimmunity and cancer

Serum IL-17 is raised in patients with MS,¹⁷ SLE,¹⁸ asthma¹⁹ and in RA synovium.²⁰ It has been shown that there is increased IL-23 secretion from monocyte derived dendritic cells from MS patients compared to healthy controls and that there is increased IL-17 production by



Dr Claire Helliwell,
Honorary Clinical Fellow,
Department of Clinical
Neurosciences,
Addenbrooke's Hospital,
Cambridge, UK.
Email: ch74@cam.ac.uk

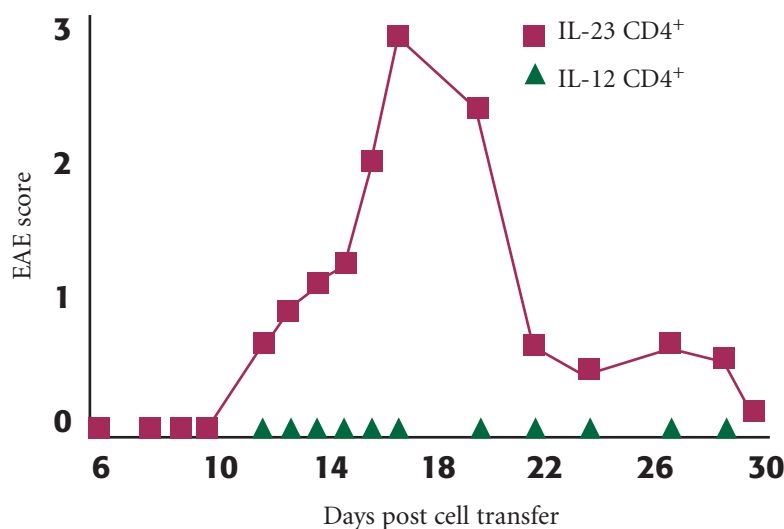
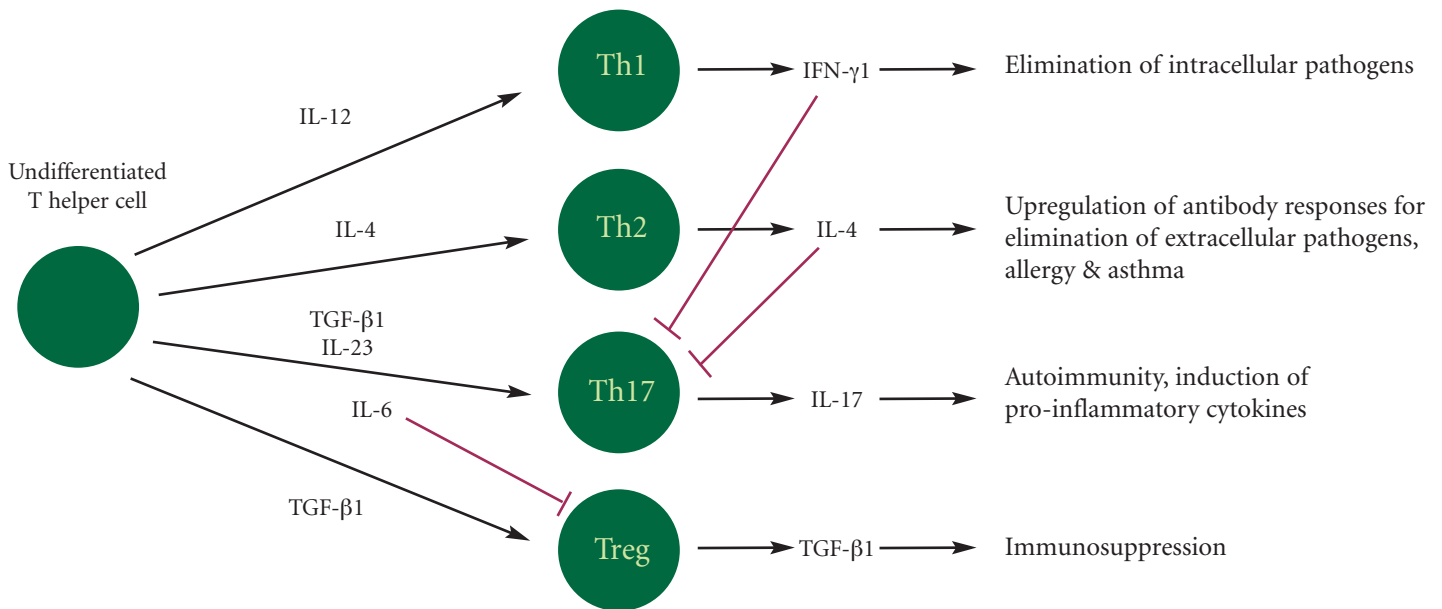


Figure 1 shows CD4+ T cells cultured *in vitro* with IL-23 (■), but not IL-12 (▲) induce EAE pathogenesis, Langrish et al.⁹



stimulated CD4+ T cells from MS patients.² IL23 may also play an important role in tumours as IL-23p19 mRNA expression has been shown to be increased in a variety of human tumours.²² One mechanism for this may be that IL-23 reduces the ability of CD8+ T cells to infiltrate tumours as shown in mice.²² At present a clear role for the IL-23/IL-17 pathway in response to infection has not been identified. IL-23 knock-out mice are less prone to some infections (tuberculosis and toxoplasmosis) than IL-12 knock-outs,^{10,23} suggesting that it may not play an important role.

Summary

Newly described Th17 cells which produce IL-17 and are expanded in the presence of IL-23 are likely to have an important role in the pathogenesis of autoimmune diseases and possibly some cancers. Work done with mice has shown that EAE is prevented by the use of anti-IL23p19 antibodies²⁴ and that anti-IL 17 antibodies give partial protection.⁹ In theory the selective neutralisation of the IL-23/IL-17 immune pathway (with an IL-23p19 or IL-17 antibody) might reduce autoimmunity, yet have little detriment on the immune response to infection.

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