



**Figure 1 | Development of the  $T_H17$ -cell lineage.** Some bacterial and fungal pathogens are detected by dendritic cells, which process them and present them as antigens, together with proinflammatory cytokines, to naive T-cell precursors. Three research teams<sup>1–3</sup> now find that dendritic-cell-derived IL-6, and another cytokine, TGF- $\beta$ , then direct the antigen-activated precursor T cell down the  $T_H17$  developmental pathway by inducing the expression of IL-21. This cytokine amplifies its own production by an autocrine feedback loop and drives the expression of the  $T_H17$ -specific transcription factor ROR- $\gamma$ . In turn, ROR- $\gamma$  induces the expression of the receptor for IL-23 — a cytokine that further enforces  $T_H17$ -cell differentiation.

receptor (ROR)- $\gamma$  (refs 5–8). This gene transcription factor prepares  $T_H17$  cells to respond to IL-23, a third cytokine that had already been associated with  $T_H17$  differentiation<sup>9</sup>.

Unlike  $T_H1$  and  $T_H2$  cells,  $T_H17$  cells had not been found to produce cytokines that reinforce their own differentiation, apparently being unable to beget their own kind through an autocrine mechanism. The three new papers<sup>1–3</sup> rectify this misconception, showing that IL-21, whose expression is induced in developing  $T_H17$  cells by dendritic-cell-derived IL-6, could sustain and amplify  $T_H17$ -cell differentiation through an autocrine feedback loop, bypassing any further requirement for IL-6.

In addition to promoting  $T_H17$ -cell differentiation, TGF- $\beta$  promotes the differentiation of a subset of T cells known as induced regulatory T ( $T_{reg}$ ) cells. In contrast to effector T cells,  $T_{reg}$  cells are responsible for maintaining immune tolerance: they limit responses mediated by effector T cells that could injure host tissues. To shift TGF- $\beta$ -induced  $T_{reg}$  development towards  $T_H17$  requires IL-6. So Korn *et al.*<sup>2</sup> predicted that, in IL-6-deficient mice, both the development of  $T_H17$  cells and the induction of a mouse model of multiple sclerosis would be impaired, instead favouring  $T_{reg}$  development. This proved to be the case. However, when the authors depleted IL-6-deficient mice of  $T_{reg}$  cells, the development of  $T_H17$  effector cells was partially restored, indicating an IL-6-independent pathway to  $T_H17$  differentiation. By screening for cytokines that might substitute for the effect of IL-6, they identified IL-21.

In complementary studies, Nurieva *et al.*<sup>1</sup> and Zhou and colleagues<sup>3</sup> compared the total gene expression of T helper cells that had differentiated under different conditions. Both teams found that, under conditions known to promote  $T_H17$ -cell development, levels of messenger RNA for IL-21 were enhanced, indicating induction of its encoding gene. These groups<sup>1,3</sup> also found that IL-21 was as effective in inducing the expression of ROR- $\gamma$  and the

receptor for IL-23 as was IL-6. But, compared with IL-6-deficient T cells, cells deficient in IL-21 were profoundly impaired in inducing IL-23 receptor, ROR- $\gamma$  and IL-17 in response to IL-6. Thus, IL-21, not IL-6, seems to be the main inducer of the IL-23 receptor.

Could IL-21 induce its own expression through a ROR- $\gamma$ -independent pathway? Possibly; ROR- $\gamma$ -deficient T cells expressed normal levels of IL-21, but expressed reduced levels of IL-17A, IL-17F and IL-22 (refs 1, 3). This indicates that, in the molecular-signalling pathway, IL-21 induction is upstream of, and independent of, ROR- $\gamma$ .

Together, these studies support a revised model of  $T_H17$ -cell development. Thus, IL-21 is both necessary and sufficient for the differentiation of  $T_H17$  cells, acting downstream of IL-6 and upstream of ROR- $\gamma$  to promote the expression of the IL-23 receptor. This, in turn, prepares cells for IL-23-mediated completion of  $T_H17$ -cell differentiation (Fig. 1).

It was known that IL-21 suppresses the production of another cytokine, IFN- $\gamma$ , both by cytolytic T cells, which destroy infected cells, and by  $T_H1$  cells<sup>10</sup>. It is therefore plausible that, in promoting the development of  $T_H17$  cells, another function of IL-21 is to suppress IFN- $\gamma$ , which can potentially inhibit  $T_H17$ -cell differentiation.

The possibility that IL-21 is an essential inductive and maintenance factor for  $T_H17$ -mediated immune responses raises the prospect that it will be a target for therapeutic intervention, either to curb the pathogenic (autoimmune) effects of  $T_H17$  or to enhance its protective (anti-pathogen) effects. ■

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1. Nurieva, R. *et al.* *Nature* **448**, 480–483 (2007).
2. Korn, T. *et al.* *Nature* **448**, 484–487 (2007).



## 50 YEARS AGO

The General Board of the Faculties of the University of Cambridge has prepared a report outlining a course whereby students could undertake study of a science subject as well as of an arts subject... The new course would give students the advantages of training in both arts and science. Arts men are trained not only to collect accurate data and to use them systematically, but also to exercise critical judgment upon matters of opinion where scholars may reach quite different conclusions. On the other hand, the conclusions of the scientist are based on precise observations and measurements, involve exact calculations, and must be tested by experiment or controlled observation; agreement on essential issues can therefore ultimately be reached.

From *Nature* 27 July 1957.

## 100 YEARS AGO

We learn with regret of the death of Prof. Egon von Oppolzer at the early age of thirty-seven. Dr. von Oppolzer, who was a son of the celebrated Theodor von Oppolzer, was born at Vienna in 1869, and was educated at the universities of Vienna and Munich. In 1897 he became an assistant in the observatory at Prague, where he discovered in 1901 the variability in the brightness of the planet Eros... Among the subjects on which he wrote are astronomical refraction, solar physics, and the application of physical theory to stellar problems. He also made contributions to meteorology. A new form of zenith telescope was constructed by him, as well as a photometer of novel design. The variability of the minor planets, which has recently become a subject of very great interest, has naturally been investigated with the greatest success by the aid of photography, and it is worthy of note that Dr. von Oppolzer's important discovery in this branch of research was established by visual observations.

From *Nature* 25 July 1907.

50 & 100 YEARS AGO