Th1/Th2 cross-regulation and the discovery of IL-10

In the late 1980s, Tim Mosmann and colleagues isolated functionally distinct T helper (Th)-1 and Th2 clones, and provided evidence that these two subsets were mutually inhibitory. Knowledge of the inhibition led to the discovery that Th2 cells make IL-10 to suppress Th1 cells.

In 1971, C.R. Parish showed that a B cell (humoral) response depended on the interaction between T and B cells. In the absence of such an interaction, T cells mediated delayed type hypersensitivity (DTH; a form of cell-mediated immunity) instead (1). Both of these functions were soon attributed to CD4+ T cells, which by then were thought to be a heterogeneous population (2).

Building a model
But direct proof of multiple CD4+ T cell subsets was a long time in coming. Until the mid-1980s, the field lacked two critical techniques: the ability to generate and maintain long-term T cell clones in vitro; and assays to detect and measure T cell–secreted cytokines.

By 1986, Mosmann, then at DNAX Research Institute (Palo Alto, CA), had the necessary techniques. Working with Robert Coffman, his team surveyed 50 clones for the expression of 7 cytokines, and separated them into Th1 clones secreting IL-2 and IFNγ, and Th2 clones producing a growth factor (later identified as IL-4) for B cells and mast cells (3).

This clonal dichotomy backed up Parish’s findings from the previous decade. The Th1 cytokines promoted DTH, whereas the Th2 cytokines enhanced immunoglobulin (Ig) synthesis and class switching (4). Furthermore, the Th1-derived cytokine IFNγ inhibited the proliferation of Th2 but not Th1 clones (5).

“Here was a mechanism to explain how an immune reaction got polarized into a Th1 or Th2 response,” says Mosmann. The clones secreted cytokines that were both autocrine growth factors and suppressors of the proliferation and activity of the opposite cell type. A breakdown in this Th1/Th2 balance might explain why some immune reactions had fatal outcomes.

Finding a “friendly” cytokine
Mosmann’s group set about finding the reverse link—a Th2-derived cytokine that would inhibit IFNγ synthesis by Th1 clones. Success came at stunning speed. Before research technician David Fiorentino had finished his first week in Mosmann’s lab, he found that all of the activated Th2 clones secreted a factor that blocked IFNγ synthesis. They called it “cytokine synthesis inhibitory factor” (CSIF).

The mystery factor perfectly fit the profile of a cross-regulator: it did not inhibit Th2 cytokine synthesis; it was not made by Th1 cells; and it inhibited production of Th1 cytokines other than IFNγ, such as IL-2 and TNF. The novel activity was not removed by depletion of known cytokines such as IL-3, IL-4, and IL-5. Mosmann hoped the team had found a new suppressing cytokine; “our only worry,” he recalls, “was that this factor might turn out to be TGFβ,” a well-known suppressive cytokine. But an anti-TGFβ antibody failed to reduce CSIF activity. Mosmann’s group published their results in *The Journal of Experimental Medicine* in 1989 (6), just as they began their attempts to purify CSIF.

Protein instability drove the group from biochemistry to cloning. Kevin Moore and Paulo Vieira (then at DNAX) made cDNA libraries from Th2 clones supplied by Mosmann’s group and used expression assays to identify what was rechristened as IL-10 (7).

This project “was one of the few times when things worked exactly according to our hypothesis,” says Mosmann. From identifying CSIF to the cloning of IL-10, each step worked perfectly. “IL-10 was really a very friendly cytokine,” he says.

Colleagues at DNAX later found that IL-10 acted directly on macrophages (8), lowering their IL-12 production and thus Th1 differentiation (9). IL-10’s known functions later expanded: it is produced by both innate and adaptive immune cell types and limits not only Th1 but, in some cases, Th2 responses (10). IL-10 curbs inflammation in vivo primarily by inhibiting cytokine production by or activation of innate immune cells (9). In its absence, inflammation can escalate to tissue-damaging levels.

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