Natural and induced regulation of Th1/Th2 balance

N. A. Mitchison¹, D. Schuhbauer², B. Müller

¹ Department of Immunology, University College London, Windeyer Institute of Medical Sciences, 46 Cleveland Street, London W1P 6DB, UK
² Deutsches Rheuma Forschungs Zentrum, Berlin, Germany

Summary. Because Th1/Th2 balance is perturbed during immunological disease, the design of strategies aiming at its rectification has become a priority. The alteration of the balance in pregnancy so as to promote survival of the fetal allograft lends credibility to this aim. Attenuation of the activation signal delivered through the T cell receptor (TCR) represents a promising approach. It is supported by the high level of polymorphism in the MHC class II promoter, which regulates the natural TCR signal and thus modulates Th1/Th2 differentiation. Further support comes from the Th2 shift that occurs in JNK knockout mice, and with kinase inhibitors and anti-CD4 monoclonal antibodies applied in vitro. The approach has implications for nasal tolerance and inhibition of IL-12 production. The further range of options for Th1/Th2 modulation, which are presented throughout this issue of the journal, are here summarised and evaluated.

Background: how we got here and what we need to know

The discovery of T and B cells marked the immunology of the 1960s, as that of regulatory T cells – the CD4 compartment – did for the 1970s. During the 1980s it became clear that the regulatory compartment could be divided: the question was how the various ways of making the split could be aligned, and which of them should be given priority [24]. At that time surface markers of phenotype were just becoming available, particularly the CD45 isoforms now accepted as markers of activation/quiescence but for a time thought to characterise suppression (as discussed here by Wedderburn and Woo). Differences in broad function of CD4 T cells were emerging, in help versus suppression and in antigen-specific versus idiotype-specific activity. There was partitioning by MHC class II-restricting element, with some MHC alleles seeming to associate with help and others with suppression [47, 41]. Related to this was the growing evidence that non-MHC genes regulate the Th1/Th2 balance (the pioneering work of Howard and Liew is discussed here by Infante-Duarte and Kamradt). Then there was the growing importance of cytokines, for it was becoming evident that different types

Correspondence to: N. A. Mitchison
of cytokine were made in different types of immune response [3]. The decisive discovery was that the cytokine pattern split into just two types, Th1 and Th2, which proved highly stable in clones grown in vitro [38]. Since that time the Th1/Th2 paradigm has proved robust. It has been buttressed by the partitioning of function. Th1 cells drive chronic inflammation and provide help for the Tc cells that protect against intracellular pathogens, while Th2 cells have the same role in the antibody response (particularly for IgE, as discussed here by Biedermann and Röcken) and thus protect against extracellular pathogens. Yet in contemplating the extraordinarily successful developments reviewed in this volume we should bear in mind that the questions of alignment and priority raised in the 1980s have not been fully answered. The summary provided in Table 2 shows how far we still have to go in assessing the global importance of the various mechanisms of immunomodulation.

Flow cytometry of T cells stained intracellularly has done much to clarify the Th1/Th2 balance [4, 22], as the article here of Kelso makes clear. Most T cells in a healthy individual are at rest and do not produce detectable amounts of any cytokine. Upon neutral activation (usually with phorbol myristate acetate/ionomycin or superantigen) a proportion of these naive or memory cells begin to secrete either one of the two characteristic markers, IFN-γ for Th1 or IL-4 for Th2. The proportion of Th1 and Th2 cells varies in different immune responses and in immunological disease, and may itself be a cause as well as a consequence of disease. Hence the concept of Th1/Th2 imbalance, and the hope that therapies may be developed to rectify it.

The rough constancy of the Th1/Th2 balance in normal individuals, and its return to equality after perturbation indicate that some underlying homeostatic mechanism must operate. Its nature is unknown; but then we know remarkably little about how the CD4/CD8 ratio is controlled, or even the total number of T cells. These questions of global control which of course apply to other organs and tissues as well, are generally thought to involve “survival factors”[45]. It is entirely possible that these survival factors will eventually turn out to be cytokines that are already familiar: we simply do not know which ones operate in this way.

Rectifying Th1/Th2 imbalance is never going to be a simple matter: sometimes we do not even know what to aim for. Organ transplantation, for instance, starts by requiring suppression of the acute Th1 response, but it is antibody which poses the major threat to long-term transplant survival [14, 42]. In autoimmune models driven primarily by Th1 cells there may be requirements for IL-4 to initiate the response [20], and of antibodies to inflict tissue damage later [28]. Nevertheless, the shift in Th1/Th2 balance that occurs during normal pregnancy offers some reassurance, as described here by Shurin et al. and by Biedermann and Röcken. A Th2 shift takes place, which is thought (among several other immunological mechanisms) to promote survival of the fetal allograft [29, 52], and which is known to help the majority of rheumatoid arthritis patients [5]. The shift may result, in part at least, from increased production of IL-10 [23] and the influence of progesterone.

Is it likely that Th1/Th2 imbalance could be reversed once a disease has become established? The long-term commitment to type observed in cell lines (see articles here by Farrar et al. and by Kelso) would seem to argue against this possibility, as would also the long-term oligoclonality of T cells observed in such diseases as juvenile arthritis, discussed here by Wedderburn and Woo. However, these obstacles may not be as formidable as they seem. Although the cytokine secretion pattern of T cells driven by repeated stimulation is indeed remarkably stable, much less is known about committed cells that pass through a period of quiescence. In oligoclonal disease the extent of re-