Th1 and Th2 Cells in Health and Disease

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An optimal host response against different microbial agents requires highly specialized reactions. Viral infections are usually controlled by CD8+ cytolytic lymphocytes. Infections sustained by bacterial, protozoan, fungal or metazoan parasites are primarily challenged by CD4+ helper (Th) cells, inasmuch as these cells are able to mobilize the most appropriate counteraction according to the type of invading agent. For example, combat of extracellular parasites involves production of soluble antibodies which first neutralize invasion and then opsonize parasites for phagocytosis. In contrast, destruction of intracellular parasites requires the activation of macrophages.

The mechanisms by which CD4+ cells can mobilize different types of effector reactions remained unclear until 1986 when Tim Mosmann and Robert Coffman first introduced the concept of Th1 and Th2 cells, based on the different set of cytokines produced. Although the CD4+ Th-mediated response is much more than Th1 or Th2 (what we call ThO cells are indeed a still unexplored, but certainly heterogeneous, family of Th cell subsets), Th1 and Th2 cells represent two extremely polarized forms that markedly helped us to understand why and how the immune system responds to various pathogens. Th1 cells produce cytokines which activate macrophages which are optimal for protection against intracellular bacteria (phagocyte-dependent host response). Th2 cells are proper opponents of bacterial toxins through cytokines that favor B-cell maturation and production of appropriate antibody isotypes. More importantly, Th2 responses are highly toxic to complex microorganisms such as metazoan parasites, and at the same time inhibit macrophage activity, since attempts to destroy large parasites through Th1 responses may be harmful to the host (phagocyte-independent host response).

A combination of Th2- and Th1-type cytokines is optimal for counteracting extracellular bacteria, as antibodies first neutralize invasion and adhesion factors and then opsonize bacteria for phagocytosis.

The concept of Th1 and Th2 cells not only allows one to explain the
different types of protection, but also provides the pathogenic basis for several immunological diseases. Strong evidence suggests that Th2 responses against common environmental allergens are responsible for allergic disorders, whereas Th1-dominated responses are involved in other hypersensitivity reactions, such as contact dermatitis, as well as in the majority of organ-specific autoimmune diseases. Thus, although clinical situations are usually more complex than suggested by either experimental animal models or in vitro studies, this paradigm offers the possibility to design novel approaches for immunointervention in different diseases. Since the concept of Th1 and Th2 cells was introduced, rapid progress in the knowledge of their physiology was achieved. In 1991, my laboratory provided definite evidence that CD4+ Th subsets similar to those described in mice do exist in humans as well. In the subsequent years, it was independently and contemporarily demonstrated in both mice and humans that IL-4 is the critical factor for Th2 cell development, whereas IL-12 is required for Th1 development. More recently, it was found that the peptide ligand density on the antigen-presenting cell and the engagement of co-stimulatory molecules, such as B7 and CD30 ligand, can also influence the type of response. Finally, the existence of surface molecules preferentially or selectively expressed by Th1 and Th2 cells is being demonstrated. For example, CD45R is differently expressed on murine Th1 and Th2 cells and the chain of the IFN- receptor is selectively expressed on murine Th2 cells. Likewise, in human cells the CD30 activation antigen appears to be preferentially expressed by those producing Th2-type cytokines, whereas another activation antigen, LAG-3, is preferentially associated with the production of Th1-type cytokines.

Several critical questions still remain to be answered. What is the relative contribution of the immunogen and of the genetic background in evoking Th1- or Th2-dominated response? What factors other than IL-12 are required for Th1 development? Which is the source of IL-4 required for Th2 development and what factors other than IL-4 are involved? What factors are responsible for intracellular signalling during Th1 or Th2 development? What or how are these polarized response states maintained? Is it possible to change the cytokine profile of established responses?

In this volume, we are accompanied on the road from basic concepts to clinical application of the Th1/Th2 paradigm by outstanding immunologists who provide an interesting 'state of the art' and suggest the next strategies for future research. I am convinced that their contributions have assembled a very interesting volume that will help all of us better understand how to direct immune responses to the type of effector function that would be most useful in eliminating or preventing a given type of infectious disease, and diminishing immunologic tissue damage in autoimmunity and allergy. It is in these very important areas that one anticipates considerable progress in the near future. I would like to thank them for sharing
their views and their interesting thoughts with all other members of the scientific community. Sergio Romagnani

Preface XII