The TH1/TH2 concept and its relevance to renal disorders and transplantation immunity

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Introduction

T cells expressing CD4 molecules on their membrane (CD4⁺ T cells) play an essential role in the orchestration of immune defences, as dramatically illustrated by the profound immunodeficiency caused by the HIV virus, which preferentially infects CD4⁺ cells. Indeed, CD4⁺ T cells are required for the induction of cell-mediated immune responses involving activated macrophages or cytotoxic CD8⁺ T cells as well as for the activation of B cells and their differentiation into antibody-producing cells. Most of these CD4⁺ T cell functions are exerted through the secretion of cytokines.

The definition of two major populations of CD4⁺ cells designated as TH1 (type 1 helper T cells) and TH2 (type 2 helper T cells) derived from the pioneer studies of Mosmann et al., demonstrating that mouse CD4⁺ T cell clones generated in vitro produce distinct sets of cytokines [1]. The TH1 clones preferentially synthesize interleukin-2 (IL-2), which is a major growth factor for all T cells, and interferon-gamma (IFN-γ), which is responsible for the activation of macrophages, whereas the TH2 clones preferentially secrete IL-4, IL-6, IL-10, and IL-13, which are growth and differentiation factors for B cells, and IL-5, which is involved in the differentiation and activation of eosinophil polymorphonuclear cells (Figure 1).

TH1 and TH2 cells were subsequently identified in vivo in experimental models of infectious diseases. The best example is that of murine leishmaniasis in which CD4⁺ T cells differentiate into either TH1 or TH2 cells, depending on the genetic background [2]. Mouse strains developing TH1 cells display strong protective cell-mediated immunity against the parasite, resulting in a self-limiting cutaneous disease, whereas mouse strains developing TH2 cells display high levels of non-protective antibodies associated with low-grade cell-mediated immunity, and die from a systemic form

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of the disease. Both in vitro and in vivo, TH1 and TH2 cells exert reciprocal antagonistic effects: TH2 cells inhibit TH1 cell functions through the secretion of IL-10, which acts mainly as a macrophage-deactivating factor, while IFN-γ secreted by TH1 cells inhibits the differentiation and proliferation of TH2 cells and also antagonizes the effects of IL-4 on its targets. This cross-regulation between TH1 and TH2 cells explains why cell-mediated immunity involving TH1 cells is often associated with low antibody production (e.g. in mycobacterial diseases), whereas increased production of antibodies might be associated with deficient cellular immunity (e.g. in visceral leishmaniasis).

It is important to realize that TH1 and TH2 cells do not pre-exist in immunologically naive individuals; indeed, they differentiate from single CD4⁺ cell precursors as a consequence of persistent antigenic stimulation [3] (Figure 1). During normal immune responses where antigens are rapidly eliminated, activated CD4⁺ T cells usually do not display a polarized TH1 or TH2 phenotype but secrete a mixture of TH1-type and TH2-type cytokines (TH0 phenotype). This is the reason why the unambiguous demonstration of TH1- and TH2-like cells in man required studies on patients suffering from chronic diseases such as parasitic infections or allergic disorders. Although TH2 clones have occasionally been observed in vivo [4], it is often very difficult to determine whether the preferential production of TH1 or TH2 cytokines in immunopathological settings is related to the presence of terminally differentiated TH1/TH2 cells or to an imbalance in the relative proportions of TH1-type or TH2-type cytokines secreted by TH0-like cells. Moreover, CD8⁺ T cells may also differentiate into polarized subsets secreting either IFN-γ or IL-4 and IL-10 [5]. It seems therefore more appropriate to use the concept of TH1/TH2 responses instead of TH1/TH2 cells when discussing the pathogenesis of diseases mediated by T-cell-derived cytokines.

Delayed type-hypersensitivity (DTH) represents the prototype of TH1 responses in vivo: as a matter of fact DTH involves CD4⁺ T cell-derived IFN-γ (a typical TH1-type cytokine) leading to macrophage activation; as expected from the cross-regulation between TH1 and TH2 responses, DTH is inhibited by the TH2-type cytokines IL-4 and IL-10. On the other hand, atopic diseases and helminth infections in which hyperproduction of IgE antibodies is associated with hyperesinophilia represent good examples of TH2-type reactions. Indeed the TH2-type cytokines IL-4 and IL-5 are responsible for IgE synthesis and eosinophil differentiation respectively.

The factors promoting TH1 or TH2-type responses
[6]

Several factors have been shown to regulate the preferential production of TH1-type or TH2-type cytokines in the course of an immune response, including the dose of antigen, the nature of the antigen-presenting cells, and the presence of certain hormones during the initial phase of antigen recognition by T cells. For example, both glucocorticoids and substances elevating intracellular cAMP (such as PGE₂) favour TH2-type responses. However, the critical factors determining the final differentiation of CD4⁺ T cells appear to be the cytokines produced in the very early phase of the immune response. As shown in Figure 1, IL-4 is the major factor promoting TH2-type responses. The cellular source(s) of IL-4 secreted immediately after antigenic challenge might include mast cells and a particular subset of CD4⁺ T cells. On the other hand IFN-α and IL-12 produced by macrophages promote TH1-type responses. The effect of IL-12 is in part related to its ability to induce IFN-γ production by NK cells; indeed IFN-γ also favours TH1-type responses.

TH1/TH2 responses in renal diseases

Although few data are available regarding the profile of cytokines produced by T cells in human nephropathies, there is evidence from experimental models that the TH1/TH2 concept might be relevant to renal immunopathology. Indeed DTH presumably related to a TH1-type immune reaction appears to be an important effector mechanism in some autoimmune tubulointerstitial nephritides such as those induced in guinea-pigs or in the Lewis rat by immunization with basement membrane antigens [reviewed in ref. 7]. Interstitial nephritis involving a DTH reaction can also occur after immunization with non-renal antigens, as shown in rats immunized against bovine gammaglobulins [8] or azobenzene arsonate [9]. The latter model is particularly interesting since it was induced by in situ delivery of the antigen, demonstrating that antigen-presenting cells within the kidney can directly trigger presensitized T cells to elicit a granulomatous DTH reaction. TH1-type responses are involved in another model of interstitial nephritis where T cells react against an inducible heat-shock protein [10] and probably also in autoimmune crescentic glomerulonephritides where CD4⁺ cells participate in the recruitment and activation of macrophages in the glomeruli such as in the model induced by injection of a subnephritogenic dose of sheep anti-rat glomerular basement membrane antibody in WKY rats presensitized to sheep immunoglobulins [11]. On the other hand TH2-type responses appear to play a pathogenetic role in models of glomerulonephritis associated with systemic autoimmunity [reviewed in ref. 12]. Typical examples are represented by the host-versus-graft (HVG) disease in mice and mercury-induced autoimmunity in rats. HVG disease is induced by the injection of newborn BALB/c mice with semi-allogeneic (A/J × BALB/c) F1 spleen cells. It is characterized by (1) a polyclonal B-cell activation with serum hyper IgE and occurrence of several autoantibodies, and (2) a membranous glomerulonephritis complicated by the late development of focal
and segmental glomerulosclerosis. The basic mechanism of HVG disease is the activation of F1 donor B cells by alloreactive host TH2-like CD4+ T cells. We recently demonstrated that the TH2 polarization of the alloreactive response in the newborn is related to the early production of IL-4 by neonatal T cells [13]. Mercury-induced glomerulonephritis in susceptible strains of rats (BN) is also associated with the occurrence of TH2-like CD4+ T cells which elicit polyclonal B cell activation resulting in serum hyperIgE and production of autoantibodies. These TH2-like cells appear to be autoreactive as they recognize self class II-MHC molecules and are able to transfer the disease in CD8+ cell-depleted naive recipients [Sauoui et al., unpublished findings]. Interestingly, mercury-induced glomerulonephritis is spontaneously regulated by ‘suppressor’ cells which belong to the CD8+ or the CD4+ subset. In the latter case, the suppressor CD4+ cells express a surface marker of TH1-type cells, suggesting that the TH2-like cells that mediate the disease can be controlled by TH1-like cells [14]. Recent experiments by Pringent et al. (manuscript in preparation) indicate that the TH2-type responses induced by mercury might be related to the ability of this compound to rapidly trigger IL-4 production by mast cells and T cells in susceptible animals. Similar mechanisms are probably operative in other models of toxic glomerulonephritis such as the one induced by gold salts.

**TH1/TH2 responses in transplantation immunity**

While both TH1-type and TH2-type cytokines seem to be produced during acute cellular rejection of allografts, TH2-type cytokines were shown to be preferentially expressed in several experimental models of transplantation tolerance such as those induced by neonatal exposure to alloantigens [13], donor-specific transfusion, or administration of anti-CD4 monoclonal antibody [reviewed in ref. 15]. It has been proposed that the non-aggressive CD4+ T cells, which are commonly observed in non-rejecting human renal allografts, might belong to the TH2 subset, but this has not yet been established. Indeed it is still unclear whether TH2-type cytokines such as IL-4 and IL-10 can actively contribute to allograft acceptance. One could even think that these cytokines might favour antibody-mediated chronic rejection by promoting B-cell activation and differentiation. Further studies are therefore needed to determine whether deliberate induction of TH2-type responses represents an efficient strategy to prevent allograft rejection.

**Concluding remarks**

The TH1/TH2 concept might help to improve our understanding of the pathogenesis of several pathological processes affecting the kidney. TH1-type responses are likely to be involved in renal disorders related to DTH reactions such as (1) certain tubulointerstitial nephrites, especially those associated with the formation of granulomas, (2) certain crescentic glomerulonephritis, especially those associated with CD4+ cell infiltration, and (3) acute allograft rejection. TH2-type responses might be responsible for renal disorders related to autoantibody formation and/or associated with IgE hyperproduction, such as certain drug-induced glomerulonephritides. Since TH1-type and TH2-type responses can be differentially modulated by pharmacological agents, including recombinant cytokines, the TH1/TH2 concept might lead to new therapeutic approaches in nephrology and transplantation.

**References**


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