Review Article

T-cell response to bacterial agents

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Abstract

T-cell responses are crucial for the outcome of any infection. The type of effector T-cell reaction is determined by a complex interaction of antigen-presenting cells with naive T cells and involves genetic and environmental factors, including the type of antigen, cytokines, chemokines, co-stimulatory molecules, and signalling cascades. The decision for the immune response to go in a certain direction is based not on one signal alone, but rather on many different elements acting both synergistically and antagonistically, and through feedback loops leading to activation or inhibition of T cells. In the course of evolution different types of T cells have developed, such as T helper 1 (Th1) cells, which protect against intracellular bacteria; Th2 cells, which play a role against parasites; and Th17 cells, which face extracellular bacteria and fungi.

Key words: microbes; T cells; cytokines; chemokines; Th1; Th2; Th17

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Introduction

In all infectious diseases, besides the virulence of the pathogen, both the natural and the specific immune responses of the host are crucial for determining the outcome of the infection. The immune system has evolved different defence mechanisms against pathogens. The first defensive line is provided by "natural" immunity, including phagocytes, T cell receptor (TCR) $\gamma\delta^+$ T cells, natural killer (NK) cells, mast cells, neutrophils and eosinophils, as well as complement components and pro-inflammatory cytokines, such as interferons (IFNs), interleukin (IL)-1, IL-6, IL-12, IL-18 and tumor necrosis factor (TNF)-α. The more specialized TCR $\alpha\beta^+$ T lymphocytes provide the second defence wall. These cells account for the specific immunity, which results in specialized types of immune responses which allow vertebrates to recognize and clear (or at least control) infectious agents in different body compartments. Viruses growing within infected cells are face the killing of their host cells by $CD8^+$ cytotoxic T cells. Most microbial components are endocytosed by antigen-presenting cells (APC), processed and presented preferentially to $CD4^+$ T helper (Th) cells. Th cells co-operate with B cells for the production of antibodies which opsonize extracellular microbes and neutralize their exotoxins. This branch of the specific Th cell-mediated immune response is known as humoral immunity. Other microbes, however, survive within macrophages in spite of the unfavorable microenvironment and antigen-activated $CD4^+$ Th cells are required to activate macrophages, whose reactive metabolites and IFN-γ finally lead to the destruction of the pathogens. This branch of the specific Th cell-mediated response is known as cell-mediated immunity (CMI) [1,2].

Most successful immune responses involve both humoral and cell-mediated immunity, but in some conditions the two types of effector reactions tend to be mutually exclusive. $CD4^+$ Th cells can develop different polarized patterns of cytokine production , such as type-1 or Th1, type-2 or Th2, type-17 or Th17 [3-5]. Furthermore, in the last decade the existence of regulatory T cells has been demonstrated and they have been named Treg. Treg cells devoted to control immune responses to self-antigens are defined as "natural Treg cells", including natural killer T (NKT) and CD4+CD25+Foxp3+ T cells. NKT cells represent a distinct population of T cells showing properties of NK cells, but expressing α/β TCR, which specifically recognizes glycolipids often

expressed by pathogens and tumour cells [6]. NKT secrete large amounts of IL-4, IL-10, IFN-γ and transforming growth factor-β (TGF-β). It is generally accepted that Foxp3 is a master control gene for the development and function of natural CD4+CD25+ Tregs, and there is no doubt that CD4+CD25+Foxp3+ T cells originate from the thymus as a distinct T cell subset [7,8], which is mainly devoted to control self-reactive T cells that have escaped negative selection, thus ensuring peripheral tolerance to autoantigens and protecting the host from autoimmunity. However, the mechanism by which natural Tregs exert their suppressive activity is still elusive. Nevertheless, it must be noted that the T helper classification is in continual revision given that new T-cell subsets are being discovering dailyy by day, such as Th3 and IL-9-producing Th9 cells.

The Th network

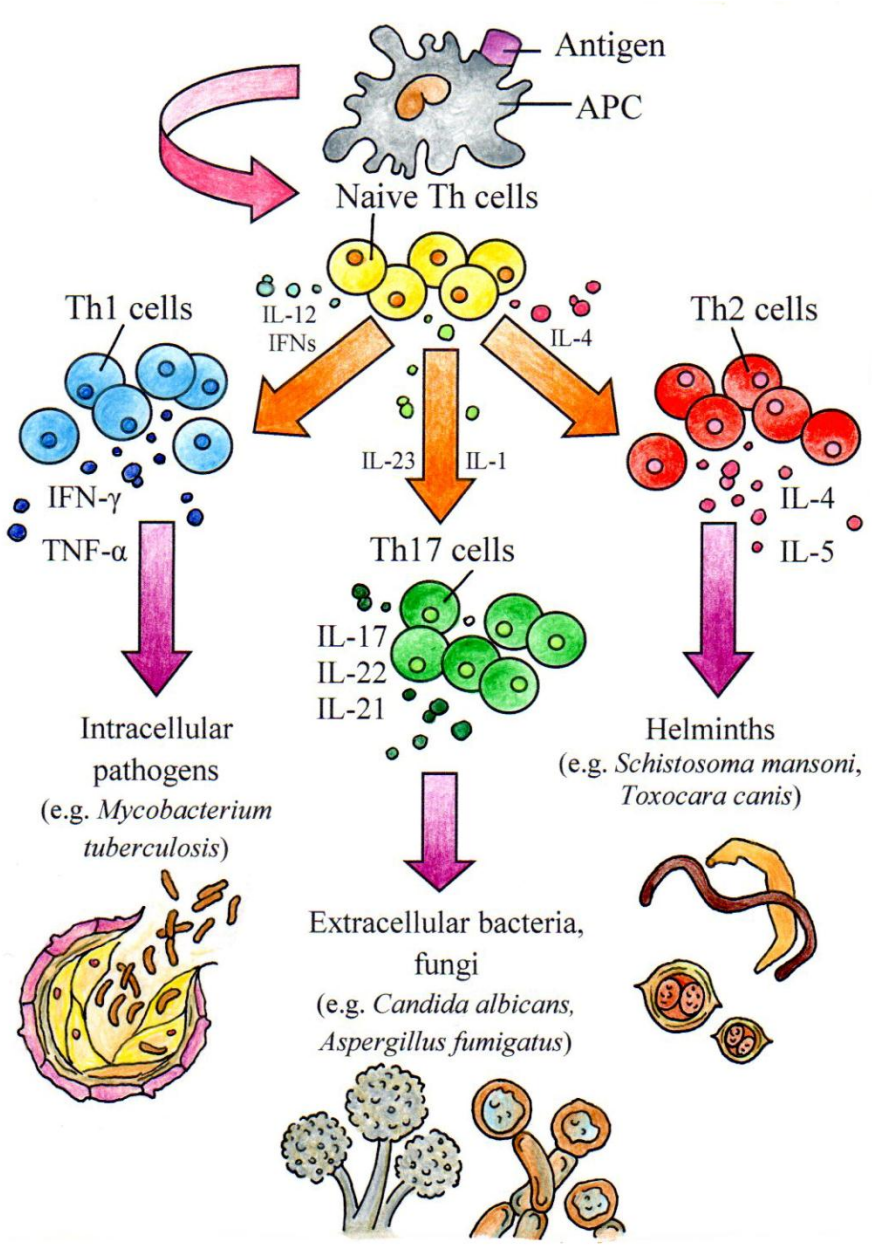
Th1 cells produce IFN-γ, IL-2 and TNF-α, as well as elicit macrophage activation and delayed-type hypersensitivity (DTH) reactions, whereas Th2 cells produce IL-4, IL-5, IL-10 and IL-13, which act as growth/differentiation factors for B cells, eosinophils and mast cells and inhibit several macrophage functions [4,9]. A similar heterogeneity in the cytokine profile was observed also in CD8+ cytotoxic T cells (Tc1, Tc2), γδ+ T cells and NK cells [10, 11]. A new subset of Th cells, named Th17 cells, producing IL-17 alone or in combination with IFN-γ, has been identified recently [12]. Th17 cells may also secrete IL-6, IL-22 and TNF-α and play a critical role in protection against microbial challenges, particularly extracellular bacteria and fungi [13].

Most T cells do not express a polarized cytokine profile; such T cells (coded as Th0) represent a heterogeneous population of partially differentiated effector cells consisting of multiple subsets which secrete different combinations of both Th1 and Th2 cytokines [14-16]. The cytokine response at the effector level can remain mixed or further differentiate into the Th1, the Th2 or the Th17 pathway under the influence of polarizing signals from the microenvironment. Human Th1 and Th2 cells also differ for their responsiveness to cytokines. Both Th1 and Th2 cells proliferate in response to IL-2, but Th2 are more responsive to IL-4 than Th1; on the other hand, IFN-γ tend to inhibit the proliferative response of Th2 cells [17].

Th cells substantially differ for their cytolytic potential and mode of help for B-cell antibody synthesis. Th2 clones, usually devoid of cytolytic activity, induce IgM, IgG, IgA, and IgE synthesis by autologous B cells in the presence of the specific antigen, with a response which is proportional to the number of Th2 cells added to B cells. In contrast, Th1 clones, most of which are cytolytic, provide B-cell help for IgM, IgG, IgA (but not IgE) synthesis at low T-cell/B-cell ratios. At high T-cell/B-cell ratios there is a decline in B-cell help related to the Th1-mediated lytic activity against antigen-presenting autologous B-cells [18]. Th1 and Th2 cells exhibit different abilities to activate monocytic cells. Th1, but not Th2, help monocytes to express tissue factor (TF) production and procoagulant activity. In this type of Th cell-monocyte co-operation, both cell-to-cell contact with activated T cells and Th1 cytokines (namely IFN-γ), are required for optimal TF synthesis, whereas Th2-derived IL-4, IL-10 and IL-13 are strongly inhibitory [19].

The factors responsible for the Th cell polarization into a predominant Th profile have been extensively investigated. Current evidence suggests that Th1, Th2 and Th17 cells develop from the same Th-cell precursor under the influence of mechanisms associated with antigen presentation [20,21]. Both environmental and genetic factors influence the Th1 or Th2 differentiation mainly by determining the "leader cytokine" in the microenvironment of the responding Th cell. IL-4 is the most powerful stimulus for Th2 differentiation, whereas IL-12, IL-18 and IFNs favour Th1 development [22-26]. A role has been demonstrated for the site of antigen presentation, the physical form of the immunogen, the type of adjuvant, and the dose of antigen [27]. Several microbial products (particularly from intracellular bacteria) induce Th1-dominated responses because they stimulate IL-12 production. IFN-γ and IFN-α favour Th1 development by enhancing IL-12 secretion by macrophages and maintaining the expression of functional IL-12 receptors on Th cells [28]. On the other hand, IL-11 and PGE2 promote Th2 cell polarization [29,30]. Th17 cells represent a distinct subset of effector T cells induced as a consequence of IL-23 production by DCs [31]. IL-23 is a heterodimer that shares the p40 chain with IL-12, but differs in the presence of a p19 instead of the p35 chain. Similar subunit sharing occurs for the IL-12R and the IL-23R: the IL-12R is a heterodimer composed of β1 and β2 chains, whereas the IL-23R contains the β1 chain but in combination with a specific receptor known as IL-23R [32].

Figure 1. T-cell response in infectious diseases



Once T helper (Th) cell recognizes a certain antigen presented by antigen-presenting cell (APC), the cytokine *milieu* plays a crucial role in driving the subsequent T-cell response. In the presence of interferons (IFNs) and interleukin (IL)-12 naive Th cells differentiate into Th1 cells (producing IFN-γ and tumor necrosis factor (TNF)-α) that are protective mainly against intracellular bacteria. In the presence of IL-23, IL-1 naive Th cells differentiate into Th17 cells (producing IL-17, IL-21 and IL-22) that are involved in protection against extracellular bacteria and fungi. In the presence of IL-4 naive Th cells differentiate in Th cells (mainly producing IL-4 and IL-5) that are protective against extracellular parasites.

Both *in vitro* differentiation of Th17 cells and *in vivo* Th17-mediated inflammation are dependent on the transcription factor retinoic acid receptor-related orphan receptor γ-t (RORγt) [33]. Some microbial products and stimuli induce a preferential activation of Th17 responses [21,34].

The response in infectious diseases

Cytokine production occurs during immune responses and can be detected in a variety of infectious or immunopathological disorders [35]. In most human infections, specific immunity is of crucial importance, but an inappropriate response may not only result in lack of protection, but even contribute to the induction of immunopathology. In human leishmaniasis, lack of IFN-γ and high IL-4 production predict progression into fulminant visceral disease, whereas individuals whose cells produce large amounts of IFN-γ usually remain asymptomatic [36]. Th1 cytokine mRNA signals were found in the skin of patients with localized and mucocutaneous leishmaniasis, whereas Th2 cytokine mRNA were highly expressed in the skin of patients with destructive forms of cutaneous or active visceral

disease [37]. Interestingly, IFN-γ in combination with pentavalent antimony was effective in treating severe or refractory visceral leishmaniasis [38].

Parasitic infections, characterized by eosinophilia and elevated IgE levels, usually elicit Th2 cytokines. Th2 responses, which down-regulate host protective Th1 functions, are less detrimental to parasites; on other hand, the host would avoid immuno-pathological reactions related to strong, but harmful, Th1 responses. The pathology resulting from *Schistosoma mansoni* infection is indeed predominantly caused by the host Th2 response leading to chronic granulomatous reaction and consequent damage to the intestine and liver [39,40].

In the immune response to bacterial infections, Th2 cells seem to be appropriate opponents against toxin-producing bacteria, since Th2 cytokines favour B-cell maturation and production of neutralizing antibodies. In contrast, intracellular bacteria (*e.g. Leisteria monocytogenes, Mycobacteria, Salmonellae*) are appropriately encountered Th1 cells, which produce cytokines able to activate macrophages and cytotoxic T cells. Mice with disrupted IFN-γ or IFN-γ receptor genes and producing high levels of IL-4 succumb to mycobacterial infections [41], whereas mice resistant to *M. bovis* produce high levels of IFN-γ and low amounts of IL-4 [42]. Likewise, patients with IFN-γR or IL-12R deficiency are extremely sensitive to mycobacterial infections and develop severe and often fatal disease [43,44]. The T-lymphocyte response to purified protein derivative (PPD) was evaluated at the clonal level in African patients with pulmonary tuberculosis (TB) before and after antimycobacterial therapy, as well as in healthy immune control subjects. In untreated patients, most PPD-specific T cells derived from either peripheral blood or pleural effusions showed a mixed Th0 cytokine profile. After six months of therapy and clinical healing, most PPD-specific T cells showed a polarized Th1 profile. The Th1 polarization was less marked in tuberculosis patients who experienced treatment failure. The cytokine profile observed after successful therapy in patients with TB was similar to that found in healthy control subjects. The Th0/Th2-biased response in African patients before therapy could be modulated *in vitro* by IFN-α or IL-12, which induced a Th1 polarization of both PPD-specific T cells. These results support the notion that active TB is associated with a predominant Th0 response to mycobacterial antigens that could play a role in the pathogenesis of the disease. Adjunctive immunotherapy using Th1-polarizing cytokines could increase host defense against mycobacteria and accelerate healing, although clinical trials in which cytokines have been used for tuberculosis have been mostly unsuccessful [45].

Th0 cells, which secrete a combination of both Th2- and Th1-type cytokines, should be the best effector cells in the immune response to extracellular bacteria since antibodies (which neutralize adhesion/invasion and opsonize bacteria) and phagocytosis are both required. The predominance of the Th1 or Th2 responses in any infectious disease is probably modulated by both the pathogen and the genetic background of the host, whose innate immunity plays a key role. Since bacteria possess several components which can trigger IL-12 production by macrophages, it is not surprising that most of them favour Th1 development. These "Th1 inducers"include the lipoarabinomannan of mycobacteria, teichoic acids of Gram-positive bacteria and lipopoly-saccharides of Gram-negative bacteria or viral polynucleotides [46]. In genetically predisposed individuals, some strong and persistent Th1 responses against bacteria may often result in immunopathological reactions, such as reactive arthritis following infection with *Yersinia entero-colitica* [47]. In *H. pylori* infection a polarized Th1 response has been documented [48]. Furthermore, it has been demonstrated that the HP-NAP protein of *H. pylori* is the major factor promoting the Th1 response [49].

In *Aspergillus fumigatus* and *Candida albicans* infection and in Lyme arthritis, a strong Th17 response has been documented and related to either protection or immunopathology [34,50,51]. Furthermore, it has been recently demonstrated that the adenylate cyclase toxin of *Bacillus anthracis* is a potent promoter of Th17 cell development [52]. The toxin selectively targets specific signalling modules in the T-cell receptor (TCR) signaling cascade through its cyclic AMP (cAMP)-increasing activity, thereby promoting Th17 cell development.

Concluding remarks

The Th cytokine network provides a useful model for explaining both different types of protection and the pathogenetic mechanisms of several immunopathological disorders. The development of polarized Th1, Th2 or Th17 responses depends on both individual genetic background and environmental factors, especially cytokines of the natural immunity at the time of antigen presentation. Th1-dominated responses are

potentially effective in eradicating infectious agents, particularly those hidden within the host cells. Th17 responses are indeed very useful for protection against fungi and extracellular pathogens. When Th responses are exhaustively prolonged, host pathology may result. Thus Th cell pathways may represent important therapeutic targets for the prevention and treatment of many infectious diseases.

Addendum

Dedicated to our beloved Professor Gianfranco Del Prete. We are all indebted to our Professor for introducing us to the exciting world of immunology research. Throughout the years he has given us both the method and his passion for research. His research has never been theoretical but always oriented to people's health, especially those suffering from neglected infectious and parasitic disease in developing countries.

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