Review Article

T HELPER SUBSETS AND INTERLEUKIN 12: ITS ROLE AS A POTENT IMMUNOMODULATOR OF CELL MEDIATED IMMUNITY

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ABSTRACT

This article reviews Interleukin (IL) IL-12 a recently described cytokine secreted by monocyte/macrophages and its interaction with T cells. IL 12 is important in the immune response by providing a link between natural resistance mediated by phagocytic cells and NK cells and adaptive immunity mediated by T4, T8 and B cells. The article also evaluates the effect of IL12 in the evolution of T helper cell subsets, its action as a bridge between innate immunity and acquired immunity and the important role it plays in modulating the cellular and humoral immune response mechanisms. Its possible role as an immunomodulator of disease is postulated.

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KEY WORDS : CMI; Immunomodulation; IL-12; T cells.

Introduction

Interleukin 12 (IL12) is a heterodimeric cytokine composed of two covalently linked chains a light (p35) and a heavy (p40) chain. IL12 is produced by monocyte macrophages, B cells and neutrophils in response to bacteria and parasites. It was initially described as an NK Cell stimulatory factor. Recently however its role in the development of TH1 cells and its role in the evolution of cell mediated immunity has been described [1].

Cells of the Immune response

The cells participating in the immune response may be divided broadly into phagocytes (monocytes, neutrophils, eosinophils), lymphocytes (T cells, B cells and large granular lymphocytes), and auxiliary cells (basophils, mast cells, platelets).

Mononuclear macrophages are progeny of pro-monocytes derived from bone marrow stem cells. monocytes released into the peripheral blood have a ruffled membrane, horse shoe shaped nucleus and contain lysosomes filled with peroxidase and acid hydrolases. Monocyte macrophages act primarily as a rapid response and the first line of defence to invaders. They process and present antigen to T & B cells. Macrophages activated by lymphokines interferon (IFN) gamma and tumor necrosis factor (TNF) alpha secreted by T cells are effectors of cell mediated immunity (CMI), with inflammatory, tumoricidal and microbicidal functions. The activation is sequential,

IFN gamma providing the initial priming and TNF alpha providing the trigger for nitric oxide and reactive peroxide release [2].

Lymphocytes are derived from bone marrow stem cells. T cells develop in the thymus and B cells develop in bone marrow. Majority of the T cells carry the TCR2 (alpha-beta) receptors (>90%), while the rest carry the TCR1 (gamma-delta) receptors. The T cells carrying the TCR -2 receptors may be CD4 positive (MHC Class II restricted T Helper cells, T4 or Th cells) or CD8 positive (MHC class I restricted T Cytotoxic cells, T8 or TC cells) [2].

The precursor of T helper cells, the Thp cells produce IL2 and differentiate into Th0 cells. Th0 cells produce IFN gamma, IL2, IL4, IL5, IL10 and are steered down a path for either Th1 or Th2 differentiation (Fig 1). Those which produce IL2 and IFN gamma have been called Th1 cells while those producing IL 4,5,6 and 10 are called Th 2 cells. Their distinctive features have been classified in Table 1 [3].

Th1 or Th2.. What Induces Differentiation

In Th1 cells the CD45 antigen is highly expressed. It helps mediate surveillance against intracellular pathogens (especially within macrophages). They require higher ligand levels for activation. They are potent macrophage activators and help the macrophage to kill intracellular pathogen. Th2 cells help in antibody production. They help in B cell proliferation, and help in formation of specific antibodies. The CD45

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Fig. 1 : Counterbalance of TH1, TH2 the Ying and Yang of CMI and humoral immunity

TABLE I
CD4 lymphocytes

Function	Th1	Th-2
Polyclonal IgG secretion	No	Yes
Help for specific Ab	No	Yes
Cytotoxicity	Yes	No
Suppressor of IgG secretion	Yes	No
DTH	Yes	No
Cytokines released	IFN Gamma, IL-2	IL-4, IL-5, IL-6, IL-10
Antigen expression of CD45	Highly expressed	Low expression
Differentiation cytokines		
Positive	IL-12	IL-10, IL-4
Negative	IL-10, IL-4	IL-12
Acts against		
(a) Intracellular pathogens	Yes	No
(b) Extracellular pathogens	No	Yes
Ligand concentration required	High ligand concentration for activation	Low ligand concentration for activation

antigen shows a low degree of expression. They function against extra cellular pathogens and require lower ligand concentration for their activity [3].

The kinetics of T cell responses seem to be regulated by the ratio of IL-12 and IL-10 levels, which may gradually decline during the immune response [4]. Th1 cells switch off Th2 cells and vice versa. IL12 is important in the immune response by providing a link between natural resistance mediated by NK cells and phagocytic cells, and adaptive immunity mediated by T4, T8 and B cells. Thus IL12 agonists or antagonists may help modulate an immune response. Once a Th1 or Th2 type response is determined early in the immune response it remains stable unless major changes take place in the balance of cytokines during the response [4].

Therapeutic implications

Immunomodulation in infections

Human immuno-deficiency virus (HIV) infection

leads to a progressive loss of CD4+ T helper (Th) type 1 cell-mediated immunity that is associated with defective in-vitro CD4+T cell proliferation and abnormal T cell death by apoptosis in response to T cell receptor (TCR) stimulation. Loss of CD4+ Th1 cell function in HIV-infected persons is not related to a Th1 to Th2 cytokine switch but to a process of activation-induced death of CD4+Th1 cells. This can be prevented in vitro by antibodies to IL-10 or IL-4, two Th2 cytokines that downregulate Th1 cell responses, or by the addition of recombinant IL-12, a cytokine that up-regulates Th1 functions [5].

IL-12 is required for the T-cell-independent triggering of NK cells by intracellular parasites and the cytokine may be useful for inducing this protective pathway in immuno-deficient hosts (6).

Immunomodulation in tumors

In mouse tumor models, IL-12 has been shown to have an immunoenhancing activity [7]. Due to its effects on T cells, recombinant IL-12 has been shown to have therapeutic activity in a variety of mouse tumor and infectious disease models and is being evaluated in clinical trials in human cancer patients. Several studies have recently suggested that immune response to malignant growths shows an enhanced Th2 subset type cytokine production and in patients with advanced cancers, this may be associated with disease progression [8]. The decrease in NK cell sub populations with elevated IL-10 and minimal IL-12 concentration in neoplastic pleural effusion would suggest the usage of IL-12 or antibody of IL-10 to improve local cellular immunity [9].

The striking therapeutic effects of IL-12 in preclinical models have led to the initiation of clinical trials to examine the potential therapeutic activity of IL-12 in human cancer patients and in patients with human immuno deficiency virus infection or with chronic hepatitis B or C virus infections [7].

IL-12 as a vaccine adjuvant

Animal experiments were carried out on mouse strains with a genetic predisposition which rendered them sensitive to *Leishmania major* due to development of nonprotective Th2 responses. They were vaccinated with parasite extracts in combination with IL-12. These mice were able to develop a protective response dominated by protective Th1 responses and successfully protected them from experimental *L.major* infection [10]. Vaccination of mice with *S.mansoni* antigen extracts and IL-12 shifts T cell differentiation towards the Th1 phenotype and protects mice from

granuloma formation and fibrosis, and thus prevents the development of Th2 responses detrimental to hosts [11].

Conclusions

IL-12 plays a very important role in the immune response by modulating Th1 and other cytokines modifying immune responses in infectious disease, malignancies, allergies and auto immunity. Its use as a vaccine adjuvant provides newer strategies in the successful therapy of human disease.

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