Cytokine and Growth Factor Reviews xxx (xxxx) xxx–xxx

Contents lists available at ScienceDirect

Cytokine and Growth Factor Reviews

journal homepage: www.elsevier.com/locate/cytogfr

Peripheral CD4+ T-cell changes in connective tissue diseases

Krisztina Vincze, Abigel Kolonics-Farkas, Aniko Bohacs, Veronika Müller*

Department of Pulmonology, Semmelweis University, Budapest, Hungary

ARTICLE INFO

Keywords:
CD4+ T cells
Connective tissue disease
Cytokines

ABSTRACT

Connective tissue diseases (CTDs) are all characterized by changes in the adaptive immune system. In the last few decades several CD4 + T lymphocytes and their products have been associated with the development, progression, organ involvement, or therapeutic response of different CTDs. The T helper (Th) T-cell subsets are easy to measure in the peripheral blood, however changes are difficult to interpret. This review summarizes data about Th1/Th2/Th17 and regulatory T-cell (Treg) changes in the most common CTDs. Concordance and divergence of data might help in the better understanding of the common processes of these different systemic autoimmune disorders and might give future clues for differences in disease behavior and treatment response.

1. Introduction

Autoimmune connective tissue disorders (CTDs) are characterized by a chronic, undulating course, increased inflammatory response against the organ structures of an organism, and the resulting symptoms. Another common characteristic of autoimmune disorders is the powerful therapeutic response to corticosteroids or other immunomodulatory substances. Systemic autoimmune diseases include systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), Sjögren's syndrome (SS), systemic sclerosis (SSc), and polymyositis/dermatomyositis (PM/DM). The etiology of autoimmune diseases is still unclear; however, the combined effect of genetic and environmental factors as well as epigenetic modifications has been suggested.

Systemic autoimmune diseases can affect any organ of an organism, although characteristic organ manifestations can be observed in each disorder. The diagnosis of systemic autoimmune diseases is confirmed by typical clinical symptoms and immunoserologic and other laboratory abnormalities. Each disorder is diagnosed based on distinct diagnostic criteria. Autoimmune diseases are challenging in many ways for the patients, including poor quality of life and excessive health impairment. One potential goal in today's modern medicine is the research for prognostic factors, which make an early diagnosis and verification of organ involvement possible, thereby achieving an early targeted treatment and the prevention of definitive organ damage. In this review we would like to summarize changes in peripheral T-cell subsets in CTDs, especially focusing on differences in CD4 + T-cell subpopulations.

1.1. The healthy immune response

A special feature of our immune system is its "intelligent" self and non-self recognition. The result of immunohomeostasis, that is, the collaboration of innate and adaptive immunity is the protection against microbes and the elimination of our own altered structures. The immune response can be divided into three phases: the afferent, central, and efferent phase. In the first afferent phase the pathogens or antigens encounter the cells (macrophages, dendritic cells, natural killer [NK] cells, granulocytes, mast cells) and humoral components (complement system, antimicrobial peptides) of innate immunity. The function of the immune cells is regulated by cytokines. The adaptive immune response starts with the activation of the antigen-presenting cells (APC, mostly dendritic cells), when they phagocytize the structure that needs to be eliminated and present the processed antigen (bound to the major histocompatibility complex or MHC) to helper (Th) and cytotoxic (Tc) T cells. After the activation of the Th cells, the released cytokines activate more T and B cells. Upon activation, B cells differentiate into plasma cells capable of immunoglobulin synthesis, which can form immune complexes with corresponding antigens or activate the complement system. The cytokines produced by Th cells affect the maturation of Tc cells to effector cells, as well as the differentiation into memory cells (Th_{mem}, Tc_{mem}, B_{mem}) [1]. Regulatory T cells (Treg) are responsible for the control of the cells of the central immune response. The elimination of the antigen/pathogen occurs in the efferent phase due to immune complex forming, cell lysis by complement activation, or destruction by activated macrophages. An interesting question remains; which part of the adaptive immune response is primarily activated in CTDs and whether the activation of the Th1 (cellular immune response) or the

* Corresponding author at: Department of Pulmonology, Semmelweis University, Diósárok u. 1/c, 1125, Budapest, Hungary.
E-mail address: muller.veronika@med.semmelweis-univ.hu (V. Müller).

https://doi.org/10.1016/j.cytogfr.2018.05.003
Received 7 March 2018; Received in revised form 10 May 2018; Accepted 16 May 2018

Th2 (humoral immune response) subpopulation of Th cells is regulated by cytokines; of particular importance is their balance in health and disease [2]. In addition, other Th subsets have been defined including T follicular helper (Tfh), Th9, and Th22. However, our review will focus only on the four major Th lineages, including Th1, Th2, Th17, and Treg.

1.2. Formation of autoimmune processes

Even under normal circumstances there are autoreactive T and B cells, as well as autoantibodies in our body. Antigen presentation of autoantigens via MHC molecules leads to the activation of T-lymphocytes; however, instead of an attacking immune response, a tolerating response occurs in the effector phase. Both passive (the presented antigen cannot trigger the next steps of the immune response) and active (anti-idiotypic network, immunological homunculus) processes participate in the formation of immune tolerance. Autoimmunity occurs also in physiological conditions; nevertheless, it should be differentiated from pathological tissue injury which can compromise body functions. In general, behind autoimmune mechanisms there can be cytotoxicity mediated by T cells, macrophages, and NK cells, such as immune complex deposition, hypersensitivity, increased production of cytotoxic and inflammatory cytokines, and a shift in the local Th1/Th2 balance [3].

1.3. Changes of $CD4^+$ T-cell function in CTDs

Immune cell dysfunctions are well characterized in autoimmune diseases. Physiologically, two-thirds of T lymphocytes are $CD4^+$ Th cells and one-third are $CD8^+$ Tc cells in the peripheral blood. The $CD4^+$ and $CD8^+$ cells expressing αβ T-cell receptors are the main components of the cell-mediated adaptive immunity. After the binding to APCs these T lymphocytes differentiate into effector T lymphocytes contributing to the immune response by carrying out diverse functions and by cytokine and transcription factor expression and/or release (Fig. 1).

The immune response (Th1, Th2, Th17 or Treg dominated) is highly dependent on the differentiation of the naive Th0 cells following the co-stimulation of the antigen/pathogen and the environment (cytokine milieu, transcription factors) mediated by the APC [4]. Mature naive CD4 + cells deployed in secondary lymphoid organs survey for antigens bound to MHCII molecules.

The cellular components—predominantly in the central phase—are B cells, T cells and elements of the monocyte cell lineage. As a result, polyclonal B-cell activation occurs, the number of antibody producing cells and autoantibody levels rise, and immune complexes are generated. The $CD4^+$ T cells play a crucial role in developing and maintaining the initial phase of the immune response, therefore their role in autoimmune diseases will be discussed below.

2. Role of T helper 1 (Th1) cells in CTDs

2.1. Physiological immune function

Differentiation of $CD4^+$ Th1 cells is triggered by interleukin 12 (IL-12) and type I and II interferon-γ (IFNγ) produced by dendritic cells and macrophages. The most important co-stimulatory signal, CD28, of the T-cell receptor and MHCII-bound antigen augment the T-cell receptor signal and promote proliferation and differentiation [5]. The main effector function of Th1 cells is the production of inflammatory cytokines (eg, IFNγ, tumor necrosis factor alpha [TNFα], TNFβ/lymphotoxin-α, IL-2, IFN-gamma-inducible protein 10, and monocyte chemoattractant protein-1 [MCP-1]) [6,7]. The most effective immune response against intracellular bacteria and viruses (B-cell activation, antibody-dependent cell-mediated cytotoxicity, opsonization, and complement activation) can be achieved through Th1 cells. IL-4 is the most important suppressor cytokine of Th1 cells, and it is important to note that not only changes in number and function, but the Th1/Th2 ratio is of major importance in health and disease. The main function of Th1 cells, cytokines released, and key activators and suppressors are summarized in Fig. 1.

2.2. Th1-cell changes in CTDs

The proportion, function, and cytokine secretion of Th1 cells are changed locally in autoimmune diseases, but these changes can be detected in the whole bloodstream as well; Th1 cells activate macrophages and NK-cells. Key transcription factors include signal transducer

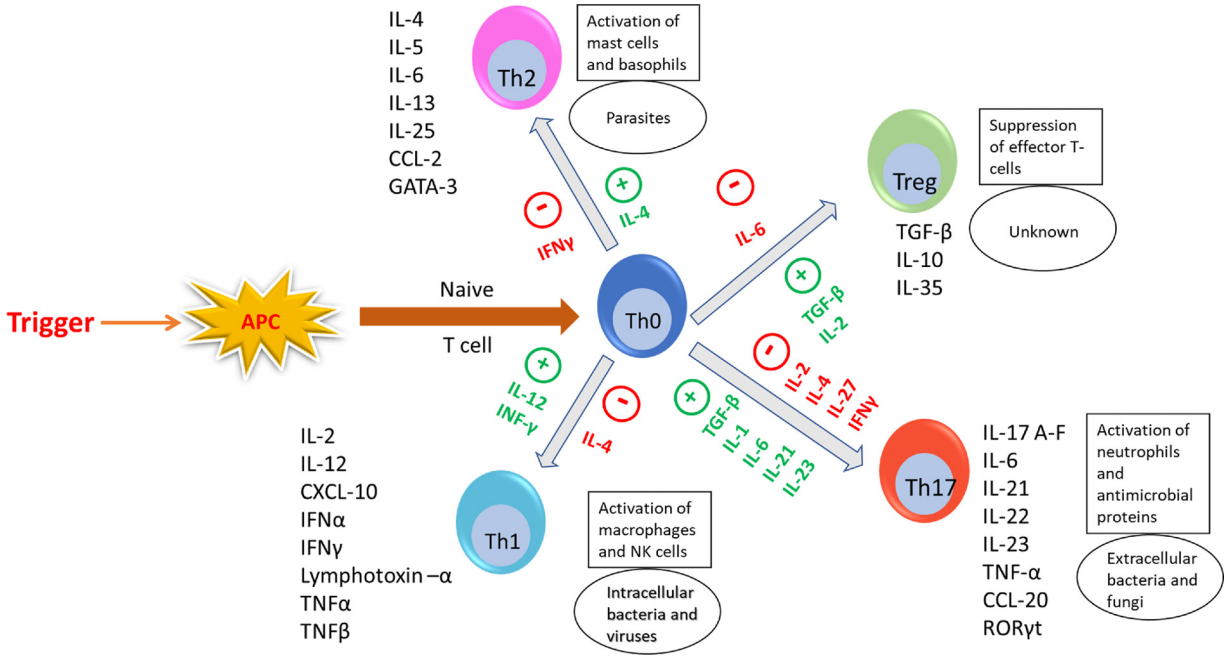

Fig. 1. Main function of Th1 cells, released cytokines and key activators and suppressors.
APC, antigen-presenting cell; CCL, chemokine (C-C motif) ligand; CXCL, IFN-γ, interferon gamma; IL, interleukin; RORγ, RAR-related orphan receptor gamma; TGF-β, transforming growth factor beta; Th, T helper cell; TNF-α, tumor necrosis factor alpha; Treg, regulatory T cell.