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Review

Targeting lymphocyte activation to treat rheumatoid arthritis

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Abstract

The introduction of targeted treatments has radically changed the management of patients with rheumatoid arthritis (RA). Abatacept is among these new treatments emerging from recent insights into joint immunopathology. Abatacept blocks the interaction between antigen-presenting cells and T-cells, thereby diminishing T-cell activation and possibly improving overall cell regulation. In RA patients, abatacept is effective in decreasing the arthritis, pain, disability, fatigue, and radiological joint damage. Abatacept provides lasting remissions or low levels of disease activity and therefore constitutes a valuable addition to the current therapeutic armamentarium for RA, which is hoped to make a full remission an attainable goal in the overall population of RA patients.

Keywords: Rheumatoid arthritis; T-cell/antigen-presenting cell interactions; Abatacept

1. Introduction

The introduction of targeted treatments has radically changed the management of patients with rheumatoid arthritis (RA). Recently developed molecular biology tools have generated approaches that shed new light on this complex disease, thereby leading to effective new treatments. Abatacept is among these new treatments that stem from recent insights into joint immunopathology.

1.1. Role for T-cells in rheumatoid arthritis

RA, which is classified among the autoimmune diseases, is the most common chronic inflammatory joint disease, with a prevalence of about 0.5%. The role for T-cells in the pathophysiology of RA has been extensively studied with the goal of understanding what triggers and perpetuates rheumatoid synovitis. That T-cells play the central role in the development of RA was challenged by Firestein and Zvaifler nearly 20 years ago [1]. These authors suggested a model in which the main culprits were activation of non-T-cells (most notably macrophage-like and fibroblast-like synovial cells) and proinflammatory mediators, whereas an antigen-specific response was of lesser importance. Although this model has been revisited [2], it highlights the many uncertainties surrounding the role for T-cells and autoantigens. Other pathogenic hypotheses for RA were developed recently in relation with the effects of new treatments targeting cytokines (TNFα antagonists, IL-1-receptor antagonists, and IL-6-receptor antagonists), B-cells (antibodies to CD20 or Blys), or the interaction between T-cells and antigen-presenting cells (APCs) (the fusion protein CTLA-4 I or abatacept). Nevertheless, animal models and data from clinical and basic studies point to a key role for T-cells and/or regulatory cells.

1.2. Rheumatoid synovitis, potential autoantigens, and T-cells

T-cells that express the memory phenotype $CD4^+CD45RO^+$ were identified in the rheumatoid synovial membrane more than 20 years ago [3]. A distortion in the T-cell repertoire has

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been found in patients with RA and may stem from an abnormality in thymic output that may allow the release of autoreactive T-cells exhibiting strong affinity for autoantigens [4]. Studies involving autoantibodies have led to the identification of many potential autoantigens in RA [5] including antigens expressed in the joint (type 2 collagen, chondrocyte glycoprotein gp39, and proteoglycans), antigens expressed only at other sites, and ubiquitous antigens (e.g., heat-shock proteins and glucose-6-phosphate isomerase). However, there is increasing interest in the role for posttranslational protein modifications in the pathophysiology of autoimmunity, via the formation of new epitopes called neoepitopes [6,7]. Citrullination of arginine residues in proteins was recently incriminated in the loss of self-tolerance in RA [8,9]. T-cell hybridoma clones specific for glycosylated epitopes were derived from DR4 transgenic mice expressing DRB*0401, a class II antigen associated with increased severity of human RA [10]. In 5 (30%) of 14 patients with severe RA, the T-cell response was confined to the glycosylated epitopes, suggesting a role for posttranslational glycosylation in the severity of RA [10].

2. Lymphocytes and cell–cell interactions

Antigens are presented to T-cells by APCs, which include dendritic cells [11] and other cell types. Many interactions occur between dendritic cells and T-cells in the synovial membrane, where the formation of germinal centers has been described [12]. Dendritic cells are hematopoietic cells found in small numbers both in the lymphoid organs and in other tissues. In peripheral tissues, dendritic cells come into contact with antigens, which they carry to the secondary lymphoid organs (lymph nodes and spleen) for presentation to T-cells. They prime the antigen and load it onto the major histocompatibility complex (MHC) molecules then become potent stimulators of naive T-cells via the expression of numerous co-stimulation molecules (CD80, CD86, CD40). The T-cell/APC interaction is potentiated and prolonged by integrins, which create an immunological synapse (Fig. 1). When a class II MHC molecule presents an antigen to the T-cell receptor, a cell-activation signal is released into the T-cell. The T-cell then enters into the G1 phase of the cell cycle (initiation of activation, which may lead to division) and expresses CD40L. CD40L binds to CD40 expressed by the APC, enhancing the expression of co-stimulatory molecules at the surface of the APC, which binds to CD28 on the T-cell. This induces release in the T-cell of the second signal, which triggers a cascade of activating events: (i) in the T-cell, transduction of the IL-2 gene (proinflammatory cytokine and T-cell growth factor), T-cell proliferation, and expression of the Bc12 anti-apoptotic proteins; and (ii) in the APC, further maturation and expression of co-stimulatory molecules such as B7.1/B7.2 (CD80/86). In the absence of this second signal, the T-cell becomes anergic then apoptotic.

Activated T-cells express CTLA-4, which quenches the activation process by releasing an inhibitory signal in the T-cell. CTLA-4 is also involved in regulation as a Treg marker and as a stimulator of the production of TGFβ, one of the regulatory cytokines. On the APC surface, CTLA-4 may decrease the expression of co-stimulatory molecules and induce the expression of indoleamine dioxygenase, which has regulatory effects, most notably on T-cells [13].

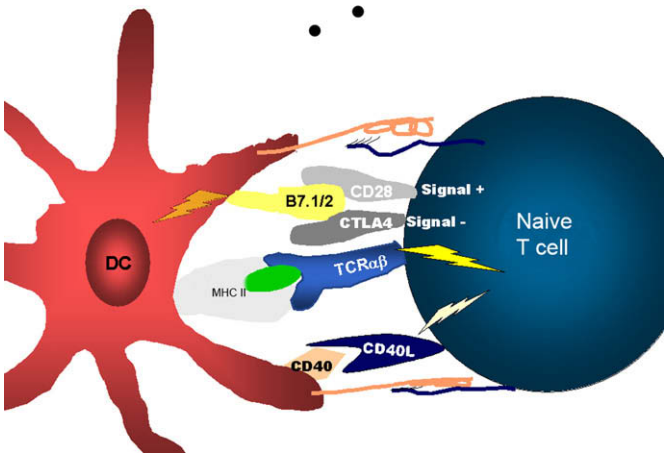

Fig. 1. Interactions between T-cells and antigen-presenting cells: The antigen (green oval shape) is loaded by a Class II major histocompatibility complex (MHC II) and presented to the T-cell receptor (TCR), which generates an activating signal directed at the T-cell. B7.1 and B7.2 (CD80 and CD86, respectively) are expressed at variable levels depending on the degree of maturation of the dendritic cell (DC). They are recognized by CD28 (positive or activating signal) or CTLA-4 (inhibitory or regulatory signal) at the surface of the T-cell. This recognition generates a signal on either side of the synapse, which amplifies or limits the activation of the DC and T-cell. The DC then expresses CD40, which is recognized by the CD40 ligand (CD40L); this generates the second activation signal, which amplifies the T-cell response. The integrins and their receptors such as LFA-1 (lymphocyte function-associated antigen 1) and ICAM-1 (intercellular adhesion molecule 1) help to ensure that contact between the antigen-presenting cell (here, the DC) and the T-cell is sufficiently tight and prolonged.

3. What is the role for T-cells in rheumatoid arthritis?

T-cells contribute about 30% of the cell infiltrate and are found in a perivascular location, suggesting migration from the peripheral blood to the synovial membrane. T-cell recruitment to the synovial membrane involves interactions with the endothelial cells lining the synovial high endothelial venules [14]. Synovitis is characterized by an imbalance in favor of proinflammatory molecules followed by deleterious activation of T-cells, which in this environment are predominantly Th1 and Th17 cells [15,16]. T-cells contribute to potentiate the autoimmune response and to activate B-cells (thereby promoting autoantibody production) in cooperation with macrophages, dendritic cells, synovial cells, and fibroblasts. In addition, T-cells interact with osteoclasts and ultimately promote the development of an autoimmune response, the production of autoantibodies, angiogenesis, and the destruction of bone and cartilage.

Incontrovertible proof that T-cells are involved in RA was obtained in studies of mutant mice lacking mature T-cells. These animals are refractory to collagen-induced arthritis.

Dendritic cells present autoantigens and maintain peripheral self-tolerance. Their role in self-tolerance depends closely on