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Review

T cell subpopulations in juvenile idiopathic arthritis and their modifications after biotherapies☆

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ABSTRACT

Inflammatory T cells are thought to be central to the pathogenesis of juvenile idiopathic arthritis. In particular, recent evidence has underlined the importance of a balance between Th17 and Treg cells. Several mechanisms have come to light that control this reciprocal relationship. Moreover, it has been shown that in certain conditions, Th17 cells can shift toward a nonclassic Th1 phenotype. Anti-rheumatic biologic therapies may interfere with these mechanisms and re-establish immune tolerance.

Contents

1. Introduction

Juvenile idiopathic arthritis (JIA) is the most frequent rheumatic disease of childhood, and is defined by the presence of arthritis of unknown cause for over 6 weeks in children under the age of 16 years [1]. Both rheumatoid arthritis and juvenile idiopathic arthritis can be severe and often need second line treatments including biologics; their pathogenesis has been the object of many studies, and identification of new targets is fundamental in order to design more specific therapies [2–6]. Different cell types of both innate and adaptive immunity (such as monocytes/macrophages, granulocytes, T and B lymphocytes) have been involved in joint tissue damage and contribute to trigger and maintain inflammation directly and/or via activation of tissues' resident cells (i.e. synovial fibroblasts and osteoclasts). Even if the etiology of JIA is still poorly understood [1], certainly T cells are involved the pathogenesis of the disease as suggested by the predominance of CD4+ T cells in the synovial infiltrates [7]. CD4+ T lymphocytes include effector cells (Teff), devoted to protection from pathogens, and regulatory cells (Treg), which suppress the immune responses toward autoantigens and also regulate reactions against exogenous antigens when they need to be dampened. Effector CD4+ T cells can be divided into functionally distinct subsets on the basis of their cytokine production, their specific transcription factors expression and their role in the protection against exogenous offending agents. In detail, T helper type 1 (Th1) secrete interferon (IFN)-γ, express the transcription factor T-box expressed in T cells (T-bet) and protect the host against intracellular infections; Th2 cells secrete interleukin (IL)-4, IL-5 and IL-13, express the transcription factor GATA-3 and mediate host defense against helminthes; Th17 cells that selectively produce IL-17A express the transcription factor retinoic acid orphan receptor (ROR)C2, and are critical for the host defense against extracellular pathogens [8–11]. Moreover, a subset of human IL-17A-producing CD4+ T cells was also found to produce IFN-γ (Th17/Th1) and both Th17 and Th17/Th1 cells exhibited plasticity towards the Th1 profile when cultured in presence of IL-12 [11]. Human Th17 cells are contained within the CD161+

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fraction of circulating and tissue-infiltrating CD4+ T cells and they originate from CD161+ precursors present in umbilical cord blood and newborn thymus, in response to IL-1β and IL-23 [12]. Regulatory T cells (Tregs) dampen the immune response and control autoimmune reactions through different mechanisms, among which cell-to-cell contact or production of anti-inflammatory cytokines (i.e. IL-10 and TGF-β) [13]. Treg cells are essential in maintaining tolerance to self and several studies described that Tregs are functionally impaired in a variety of autoimmune diseases, leading to inefficient regulation of autoimmune T cells, because of their control of autoreactive B cells and of homeostasis of humoral immunity [14].

2. T cell subsets in synovial fluid of JIA patients

In this context, a precise characterization of T cell subpopulations present in the site of inflammation (i.e. the synovial compartment) could be important to better clarify the pathogenesis of inflammatory arthropathies, and to define if the balance between pro-inflammatory factors and immune regulation could have an impact in clinical phenotype. All of these, hopefully, will be of help in designing new specific and effective treatments for immune-mediated arthritides. Moreover, the analysis of the modifications of T cell populations during medical treatments will also be of help in understanding the mechanisms of action of drugs such as biological agents and the patient's response to different treatments.

2.1. T effector cells

At the beginning, many human autoimmune diseases were associated with a Th1 phenotype, these cells being the main subset present in the inflamed site [15,16]; following the discovery of Th17 cells, many investigators focused their attention on this subset and on its role in inflammatory and autoimmune diseases, including arthritis in both adult and child [17]. Accordingly, some authors reported increased levels of IL-17A, as well as the presence of Th17 cells and expression of their transcription factor RORC in the synovial fluid (SF) of children with JIA [18,19]. Even if the debate on the relative role of Th1 or Th17 or both T cell subsets in the pathogenesis of JIA is still open, recent findings indicate that a particular population of Th1 lymphocytes could play a crucial role in the pathogenesis of JIA.

In detail, we recently described an enrichment for CD4+ CD161+ T cells, belonging to Th1 and Th17/Th1, but not Th17 subset, in SF from children with oligoarticular JIA compared to their peripheral blood [20]. These cells have been defined as "nonclassic" Th1 lymphocytes since they are Th1 cells (producing IFN-γ alone and not IL-17) but linked to the Th17 subset because of their expression of CD161, IL-23R and RORC2. More importantly, Th17 cells from the synovial fluid of children with JIA spontaneously shifted in vitro to Th1 cells, whereas Th17 cells from the peripheral blood of healthy children did so only in the presence of synovial fluid, this effect being neutralized by blocking IL-12. These data sustain the important role of this pro-inflammatory cytokine, found at elevated levels in SF, in inducing this shift and at least in part could explain the low frequency of pure Th17 cells (not producing IFN-γ) and the prevalence of Th17/Th1, and even more of Th1 cells (part of which express CD161), in the SF of JIA children. Moreover, the results of this study also demonstrated the existence of a positive correlation between the proportions of CD4+ CD161+ Th17/Th1 cells present in the SF of affected joints and markers of disease activity such as the levels of ESR and CRP [20]. This provides further support to the concept that Th17/Th1 cells are particularly important in sustaining the chronic inflammatory process. Similar results were obtained in another paper, in which Th17/1 cells from the joints of children with inflammatory arthritis were shown to express high levels of both Th17 and Th1 lineage-specific transcription factors, RORC2 and T-bet [21]. Moreover, it has been shown that Th17 cells convert to Th17/1 under conditions that mimic the disease inflammatory environment, namely low TGFβ and high IL-12 levels. Finally, both of these papers showed that Th17/1 and nonclassic Th1 [20,21] cells from SF of the inflamed joint of JIA patients share T-cell receptor (TCR) repertoire with Th17 cells, suggesting a shared clonal origin between Th17, Th17/1 and nonclassic Th1 cells in JIA.

More recently, it has been described that Th17 cells express higher level of TNFRII than Th17/Th1 and Th1 cells (both classic and nonclassic subsets) and in particular that the pro-inflammatory cytokine TNF-α was also able to induce the shift of Th17 cells towards the Th17/Th1 and the nonclassic Th1 phenotype [22].

All these data could at least in part solve the debate on the relative role of Th17 and/or Th1 cells in the pathogenesis of JIA and other chronic inflammatory and autoimmune diseases and, in this context, the surface marker CD161 appears important to track this shift, marking Th1 cells derived from Th17 phenotype. Another sign of the Th17 origin of nonclassic Th1 cells derived from the methylation status of specific gene. Indeed, it has been demonstrated [23] that nonclassic Th1 cells, like Th17 cells, have a marked RORC2 and IL17A demethylation, whereas classic Th1 cells exhibit a complete methylation of these genes. These data confirm, at the epigenetic level, a similarity between Th17 and nonclassic Th1 cells and moreover identify, in the RORC2 and IL17A methylation status, a novel tool for their distinction from classic Th1 cells. So the demonstration of the plasticity of Th17 represents a possible explanation of the rarity of Th17 cells in the inflammatory sites in comparison with Th1 cells [24]. A second reason for this rarity is the existence of some self-regulatory mechanisms that limit their expansion. The limited expansion of human Th17 cells is related to the retinoic acid orphan (ROR)C-dependent up-regulation of the interleukin (IL)-4 induced gene 1 (IL4I1), which encodes for a l-phenylalanine oxidase that has been shown to down-regulate CD3ε expression in T cells [25]. This results in abnormalities of the molecular pathway, which are responsible for the impairment of IL-2 production and therefore for the lack of cell proliferation in response to TCR signalling. IL4I1 up-regulation also associates with the increased expression of Tob1, a member of the Tob/BTG anti-proliferative protein family, which is involved in cell cycle arrest [26].

2.2. Treg cells

In JIA, the balance between proinflammatory factors and immune regulation may have an impact on clinical phenotype, since it has been suggested that patients with a mild, remitting phenotype of JIA (persistent oligoarticular JIA) and those with a more severe disease (extended oligoarticular JIA) have different T cell populations (Tregs versus Th17) [27,28]. In particular, it has also been shown that Tregs, CD4+ CD25 high FoxP3+, are present at significantly higher numbers in the joints of children with persistent oligoarticular JIA than in those with extended oligoarticular JIA, and that the proinflammatory T cell subset that produces IL-17, IL-21 and IL-22 (the Th17 subset) is enriched in the joints, compared with the blood, of children with JIA [28]. This latter cell type is found in significantly higher numbers in the joints of children with extended oligoarticular JIA than in those with persistent oligoarticular JIA [24]. Finally, it has also been demonstrated that these two specific T cell subpopulations (Tregs and Th17) show a directly reciprocal relationship within the joint [18,19].

In the context of mechanisms of suppression and control of immune response, it has been demonstrated that Teff cells from the inflamed synovium of patients with JIA, but not from PB of the same patients, are refractory to Treg cell-mediated suppression in terms of proliferation and cytokine production [29,30] and that the resistance to suppression correlated with the activation status of the cells. In fact, it has been demonstrated that the unresponsiveness to suppression resulted at least partially from protein kinase B (PKB)/c-Akt hyperactivation in inflammatory Teff cells.

3. Effects of biological drugs on T cell subsets

As reported in the first part of this review, in recent years, considerable progress in elucidating the mechanisms for local and systemic