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Review

The new era for the treatment of psoriasis and psoriatic arthritis: Perspectives and validated strategies

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ABSTRACT

Psoriatic Arthritis (PsA) is a chronic inflammatory arthropathy associated with psoriasis. Psoriasis (PsO) is a chronic, inflammatory skin disease, characterized by hyperproliferation and aberrant differentiation of keratinocytes. PsA and PsO can be considered as a unique disease and are immune-mediated diseases and both innate and adaptive immunity play a role in their pathogenesis. Initially, PsO and PsA were thought to be Th1-mediated diseases, however, in the last years, several studies have shown the role of interleukin 17 (IL-17) and Th17 cells in the pathogenesis of PsA and PsO. Th17 cells have been detected in dermal infiltrates of psoriatic lesions as well as in synovial fluid. Interleukin (IL)-23, produced by antigen presenting cells (APC), especially by dendritic cells (DC), is the key regulator cytokine for Th17 and IL-17 production. In this review we discuss the role of IL-17 and IL-23 in the pathogenesis of PsO and PsA and their role as therapeutic targets for PsO and PsA treatment.

Contents

1. Introduction

Psoriatic Arthritis (PsA) is a chronic inflammatory arthropathy commonly associated with psoriasis (PsO). It can affect the spine, the peripheral joints and entheses. Joint disease is characterized by systemic inflammation and extensive synovitis resulting in erosions of articular cartilage leading to joint destruction [1,2]. Progressive damage begins early in the course of the disease as a consequence of the active inflammation, and results in radiological damage up to 47% of patients at a medial interval of 2 years [3]. Radiological changes in PsA can be erosive lesions, osteolysis and also periarticular new bone formation [4]. PsA has been classified in five clinical subtypes: oligoarticular (<5 joints) asymmetric, polyarticular often symmetric, distal interphalangeal (DIP) joint predominant, spondylitis spine predominant, and arthritis mutilant. PsA pathogenesis is not completely understood and some authors have assumed that PsA is mainly an entheseal disease [5]. This hypothesis links mechanical stress (entheses) and immunologically active tissue (synovium). Microdamage to the entheses is associated with local cytokine release, tissue repair responses, and vessel ingrowth, which may evolve into subsequent inflammation. Moreover, it has been suggested that molecules derived from bacteria may be preferentially deposited at the synovial–enthesial complex. Therefore, in the presence of a certain genetic background, microdamage and bacterial molecule deposition

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may lead to the characteristic inflammatory changes seen at the entheses in PsA [6]. PsO is a common, chronic inflammatory skin disease, affecting about 2% of the worldwide population [7]. It is characterized by hyperproliferation and aberrant differentiation of keratinocytes, dilated, hyperplastic blood vessels and an inflammatory infiltration of T cells, dendritic cells, macrophages, nk cells and neutrophils [8,9]. Although the pathogenesis of psoriasis is not fully understood, there are several evidences suggesting a critical role of the immune cells, especially T cells. Several evidences proved a close relationship between streptococcal infection and psoriasis, making streptococcal antigens the main candidate responsible for activating T cells [10]. The role of T cells is underlined in psoriasis and PsA by the beneficial effect of therapies directed against T cells, such as cyclosporin A [11]. Originally, Pso and PsA have been considered to be classical Th1-mediated diseases with IFN-γ and IL-12 production; subsequently, other Th populations and their cytokines have been demonstrated to play a role in PsO and PsA. Several clinical and experimental observations indicated in the monocyte/macrophage-mediated inflammation a key factor stimulating keratinocyte and synoviocyte hyperproliferation [12]. For many years, monocyte-derived TNF-α has been considered the main immunological mediator in Pso and PsA. TNF-α is both an autocrine stimulator and a potent paracrine inducer of other inflammatory cytokines and plays a dominant role in the inflammatory cascade in various inflammatory disorders [13]. A deeper understanding of the pathogenic circuits in PsO and PsA revealed novel key cytokines and T cell subsets to be targeted. In particular, recent studies have been focused on the emerging and central role of Th17 cells and their derived cytokine, IL-17. IL-17 has been proposed as a key-player in the most relevant pathogenetic circuits, acting in synergy with TNFα [14]. A selective inhibition of TNF-α by anti-TNF agents reduces TNFα activity in both joint and skin environment. In the synovial tissue in PsA, anti-TNF agents deactivate the endothelium, with a decrease of vascularity, which reduces the migration and homing of inflammatory cells into the synovial tissue, leading to a reduction in lining layer thickness. In the skin, reverting the hyperproliferative phenotype, anti-TNF therapy restores the normal epidermal keratinocyte differentiation process. In the last years, the use of biological treatments opened new perspectives in the treatment of PsA and Pso, becoming rapidly a standard therapeutic strategy for their relatively high efficacy. However, despite anti-TNF-α agent therapeutic efficacy, the adverse effects cannot be neglected, especially the increased risk of tuberculosis infection during treatment [15]. Moreover, in PsA anti-TNF agents are less effective in maintaining response after treatment cessation, and numerous data suggest that withdrawal of anti-TNF therapy is almost invariably followed by disease recurrence [16]. A paradoxical effect of TNF-α antagonist treatment from clinical reports is the induction or exacerbation of psoriatic skin lesions [17]. The mechanisms by which TNF blockade enhances skin inflammation are not well understood. However, in a murine psoriasis-like skin disease model, it has been demonstrated that neutralization of TNFα enhances the expression of proinflammatory cytokines IL-1β, IL-6, IL-17, Il-21 and IL-22 and reduces the number of FoxP3-positive Treg cells in the draining lymph node [18]. These findings reveal an immunoregulatory role of TNFα on Th17 and Treg cells in some individuals, which may account for the exacerbation of skin inflammation in some patients who receive anti-TNF treatments. Consistent with these observations, TNF blockade has been shown to expand Th1 and Th17 cells in a CIA model [19]. Besides, some patients do not respond to anti-TNF agents or they undergo a loss of response to the treatment. Several studies have investigated the reason of anti-TNF treatment failure, focusing especially on the role that other cytokines may play in the pathogenesis of Pso and PsA, such as IL-12, IL-23 and IL-17. Thus, an increasing interest on IL-17 as psoriasis-signature mediator led to the development of therapeutics antagonizing its signaling/effects.

2. T cell subsets and IL-23/IL-17 pathway

The T cell subset differentiates to different effector lineages depending upon the local cytokine milieu [20]. In the presence of IL-12, naive T cells differentiate to Th1 cells whereas, in the presence of IL-4 they differentiate to Th2 cells [21,22]. Th1 cells mainly produce INF-γ, IL-1 and IL-2, which have pro-inflammatory activity, whereas Th2 cells produce IL-4, IL-5 and IL-10, which are anti-inflammatory cytokines [23]. In 2005, a new population of T cells was discovered; they were termed Th17 cells because of their ability to produce IL-17 [24,25].

The Th1 and Th2 cytokines inhibit the development of Th17 cells from the naive T cells whereas the committed Th17 cells are resistant to the suppression by Th1/Th2 cytokines [26]. In the absence of Th1/Th2 cytokines, other cytokines are involved in the differentiation of Th17 cells from naive T cells. There are some differences between mouse and human Th17 biology. In naive CD4+ T cells from mice, IL-17 is expressed in response to a combination of IL-6 or IL-21 and transforming growth factor-β (TGF-β) and requires induction of the transcription factors RORγt (retinoic acid-related orphan receptor) and STAT3 (signal transducer and activator of transcription 3). It has been suggested that human Th-17 cell differentiation is independent of TGF-β and thus differs fundamentally from mouse [27,28]. In mice IL-23 seems to be involved in the expansion of established Th17 population, but this cytokine alone cannot convert naive T cells to Th17 cells. In contrast to murine T cells, human T cells with a naive surface phenotype failed to produce IL-17 in presence of TGF-β and IL-6 [29,30]. However, increased expression of IL-17 was observed in response to IL-1β alone [31] or to IL-23 [32]. Other studies have failed to observe such a response in humans [33]. In 2008 it was reported that a combination of TGF-β, IL-1β and IL-6, IL-21 or IL-23 in serum-free conditions was necessary and sufficient to induce IL-17 expression in naive human CD4+ T cells from human cord blood [34]. The signature cytokine of Th17 cells is IL-17, which is encoded by a gene located on chromosome 6. There are six cytokines in the family of IL-17, named from IL-17A to IL-17F [35]. IL-17A and IL-17F are homodimers and share 55% of amino acid similarity. Both these cytokines have potent inflammatory potential and are involved in the pathogenesis of several autoimmune diseases, such as PsO and PsA and also SLE, rheumatoid arthritis and systemic sclerosis [36]. IL-17A mediates its effects through interaction with its cognate receptor, the IL-17 receptor, composed of three subunits, two IL-17RA subunits and one IL-17RC subunit. Also IL-17F uses this receptor and both these subunits to transmit signal, even though it has a stronger binding affinity to IL-17RC [37].

3. Role of IL-17 in PsO and PsA

Th17 cells were initially found to be implicated in an animal model of multiple sclerosis [38] since then, Th17 cells have been proved to be involved in the pathogenesis of type I INF-driven systemic autoimmune diseases, such as SLE, rheumatoid arthritis, systemic sclerosis, PsO and PsA [39]. Although type I INFs have been shown to antagonize Th17 responses, it is also evident from the observations made in diseases such as PsO or SLE that type I INF and Th17 responses can coexist to drive inflammation and disease [40]. From these evidences, it has been proposed that in systemic autoimmune diseases both type I INF and IL-17/Th17 responses contribute to disease pathogenesis by supporting and amplifying autoimmune B-cell responses, and recruiting and activating myeloid cells, especially neutrophils and antigen-presenting cells, and that both systems may sustain each other [41].

From studies on animal models of autoimmune arthritis (CIA), it has become clear that the IL-23/IL-17 axis plays a critical role in the development of autoimmune arthritis; in fact, mice deficient for IL-23 are protected against the development of CIA. Moreover, IL-17 knockout mice develop less severe arthritis [42,43].

IL-17 helps in osteoclastogenesis and bone resorption by inducing the expression of receptor activator of NF-kB ligand (RANKL) [44]; it