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The role of the Th17 cytokines IL-17 and IL-22 in Rheumatoid Arthritis pathogenesis and developments in cytokine immunotherapy

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ABSTRACT

Over the past few years, the importance of Interleukin (IL)-17 and T helper (Th)17 cells in the pathology of Rheumatoid Arthritis (RA) has become apparent. RA is a systemic autoimmune disease that affects up to 1% of the population worldwide. It is characterized by an inflamed, hyperplastic synovium with pannus formation, leading to bone and cartilage destruction in the joints. By the production of effector cytokines like IL-17 and IL-22, the T helper 17 subset protects the host against bacterial and fungal infections, but it can also promote the development of various autoimmune diseases like RA. Hence, the Th17 pathway recently became a very interesting target in RA treatment. Up to now, several therapies targeting the Th17 cells or its effector cytokines have been tested, or are currently under investigation. This review clarifies the role of Th17 cells and its cytokines in the pathogenesis of RA, and provides an overview of the clinical trials using immunotherapy to target this particular T helper subset or the two main effector cytokines by which the Th17 cells exert their function, IL-17 and IL-22.

1. Introducing the Th17 cells

Interleukin-17 is a proinflammatory cytokine that has already for decades been implicated in the pathogenesis of many autoimmune diseases including Rheumatoid Arthritis (RA), psoriasis and multiple sclerosis. The identification of the IL-23/IL-17 pathway in driving various autoimmune models lead to the discovery of the Th17 cell [1–4], with interesting new targeting options for therapy. Th17 cells are a subset of T cells named after their signature cytokine, IL-17. In addition to IL-17, these T cells secrete various other proinflammatory cytokines like IL-21, IL-22, granulocyte–macrophage colony-stimulating factor (GM-CSF) and tumor necrosis factor α (TNFα). The chemokine receptors expressed on the surface of Th17 cells are c-c chemokine receptor (CCR)2, CCR4, and CCR6 [5,6]. Differentiation of naïve T cells into Th17 cells is regulated by a combination of transforming growth factor β (TGF-β), also essential for the development of the anti-inflammatory regulatory T cells, and at least one of the following cytokines IL-6, IL-21, IL-1β, and IL-23 in both mice [7–9] and humans [8–12] (Fig. 1). TGF-β stimulates RAR-related orphan receptor γt (RORγt) expression by T cells while inhibiting the production of IL-17 at the same time. The aforementioned proinflammatory cytokines relieve this inhibition, thereby inducing IL-17 expression by the Th17 cells [8]. Additionally, both interferon γ (IFNγ) and IL-4, known to be key Th1 and Th2 cytokines respectively, have been shown to suppress differentiation of Th17 cells [4,13].

RA is an autoimmune disease characterized by chronic inflammation of synovial joints, leading to destruction of cartilage and bone. Accumulating evidence indicates the relevance of T cells in the pathogenesis of RA: there is an abundance of T cells in synovial tissue and fluids [14], and there is an association between specific major histocompatibility complex (MHC) class II alleles and RA [15]. Moreover, T cells play an important role in animal models of arthritis [16–18], and improvement of RA symptoms by T cell

Abbreviations: AIA, antigen-induced arthritis; CCR, c-c chemokine receptor; CIA, collagen-induced arthritis; CRP, C-reactive protein; CTLA-8, cytotoxic T lymphocyte associated antigen 8; DMARDs, disease modifying anti rheumatic drugs; ESR, erythrocyte sedimentation rate; FLS, fibroblast-like synoviocytes; G-CSF, granulocyte colony stimulating factor; GM-CSF, granulocyte-macrophage colony-stimulating factor; HSV13, herpes virus Saimiri; IFNγ, interferon γ; IL, interleukin; IL-TIF, IL-10-related T cell-derived inducible factor; mAb, monoclonal antibody; MCP-1, monocyte chemoattractant protein 1; MHC, major histocompatibility complex; MMP, matrix metalloproteinase; MTX, methotrexate; NF, nuclear factor; OPG, osteoprotegerin; PA, Psoriatic Arthritis; PBMCs, peripheral blood mononuclear cells; PGE_2, prostaglandin E2; PMA, phorbol 12-myristate 13-acetate; RA, Rheumatoid Arthritis; RANKL, receptor activator of nuclear factor κB ligand; RASF, Rheumatoid Arthritis synovial fibroblasts; RORγt, RAR-related orphan receptor γt; RF, rheumatoid factor; SCID, severe combined immunodeficient; TCZ, Tocilizumab; TGF-β, transforming growth factor β; Th, T helper; TNFα, tumor necrosis factor α; UA, Ursolic acid; VEGF, vascular endothelial growth factor; vIL-17, viral IL-17; VIP, vasoactive intestinal peptide; WT, wild type.

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directed therapeutic approaches has been observed [19]. The first association made between Th17 cells and a genetic polymorphism contributing to RA pathology, was when a SNP in the IL-4 receptor gene appeared to influence the levels of Th17 cells and cytokines. RA patients homozygous for this particular SNP showed increased serum levels of Th17 cells itself, as well as of its cytokines IL-17 and IL-22 [20]. Interestingly, levels of IL-17 producing T cells are significantly increased in peripheral blood of RA patients as compared with healthy controls, strongly correlating with the disease activity [21–24]. In addition, increased levels of Th17 cells were observed in RA synovium, as compared to synovium from healthy controls [25]. Furthermore, elevated levels of IL-22 producing CD4+ cells in the peripheral blood of RA patients were observed. A positive correlation between the levels of IL-17$^+$ and IL-22$^+$ cells was present, however only 20% of the IL-17$^+$CD4$^+$ cells also produced IL-22. Moreover, T cells producing IL-22 but not IL-17 were shown as well [21].

A recent study demonstrated that in RA patients not responding to treatment with the, overall very effective, biologicals targeting TNFα increased levels of both Th17 cells and cytokines were observed [22]. In addition, in mice it was shown that anti-TNF treatment during experimental arthritis caused an expansion of the pathogenic Th17 population [27]. Since the group of anti-TNF non-responders accounts for 30% of the RA patients, it is important to investigate other treatment options for those patients. As Th17 cells seem to be linked with anti-TNF non-responsiveness, those cells or its effector cytokines might be interesting new targets in RA therapy.

2. The key Th17 cytokine: IL-17

During a search for novel molecules exerting immune functions, the cytotoxic T lymphocyte associated antigen-8 (CTLA-8) was isolated. This molecule was shown to have a very restricted tissue distribution, as it could only be detected in mouse T cell hybridoma clones. Screening of the CTLA-8 cDNA sequence revealed an AU-rich repeat in the 3′ untranslated region of the mRNA, which was previously found in the mRNA of various cytokines, growth factors, and oncogenes. The protein showed 57% homology to a protein of the herpesvirus Saimiri (HSV13), a T lymphotropic virus [28]. A variety of cell types was shown to respond to both recombinant HVS13 and mCTLA-8 the way they respond to well-known proinflammatory interleukins. For instance, nuclear factor (NF)-κB was activated, IL-6 secretion by fibroblasts was induced, and T cell proliferation was stimulated. Hence, the new name IL-17 was proposed for mCTLA8, and viral IL-17 (vIL-17) for HSV13.

In the sequel of this discovery, a cDNA was cloned encoding human IL-17. As with the mouse IL-17 the cDNA sequence showed a high degree of homology to HVS13, and the expression profile was restricted to specific cell types: human IL-17 mRNA could only be detected in activated CD4+ T cells, but not in resting peripheral blood mononuclear cells (PBMCs), resting CD4+ T cells, CD8+ T cells, B cells, monocytes, or in various human organs [29,30]. After activation of CD4+ and CD8+ with phorbol 12-myristate 13-acetate (PMA) and ionomycin human IL-17 was solely detected in CD4+ lymphocyte supernatant. Thereby, secretion by activated CD4+ T cells of hIL-17 was confirmed at the protein level [30]. These CD4+ T cells producing the proinflammatory IL-17 have been designated later as T helper 17 cells [31].

IL-17, or IL-17A to be more specific, is the most studied family member of the IL-17 family consisting of six cytokines called IL-17A-IL-17F [32]. The function of IL-17B-E is still poorly described, but IL-17A and IL-17F have been reported to have quite overlapping functions in autoimmunity, which could be explained by their structural homology. IL-17A and IL-17F can be secreted as homodimer or heterodimer (IL-17A/F) [33] and bind to the IL-17 receptor (IL-17R) complex that is widely expressed throughout the body.

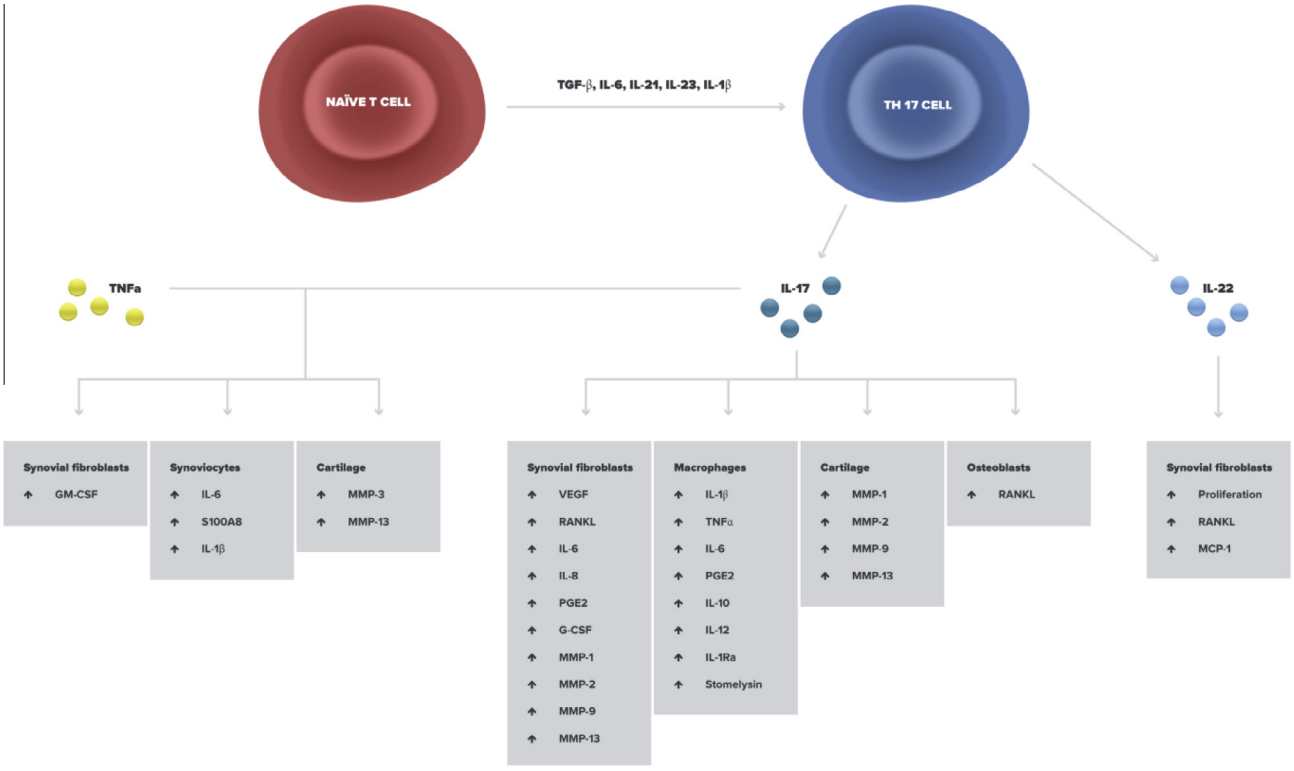

Fig. 1. Th17 pathway: differentiation and effector function. The induction of Th17 development and cytokine secretion with subsequent stimulatory actions are shown. G-CSF, granulocyte colony stimulating factor; GM-CSF, granulocyte–macrophage colony stimulating factor; IL, interleukin; MCP-1, monocyte chemoattractant protein 1; MMP, matrix metalloproteinase; PGE2, prostaglandin E2; RANKL, receptor activator of nuclear factor κB ligand; TGF-β, transforming growth factor β; Th, T helper; TNFα, tumor necrosis factor α; VEGF, vascular endothelial growth factor.

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