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# Th17-Cells in the Pathogenesis of Rheumatoid Arthritis

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## Abstract

Naive CD4+ T cells, upon activation by antigen-presenting cells (APCs) and several cytokines, differentiate into different lineages of effectors Th subtypes, which play a central role in modulating immune response. While, Th1 and Th2 cells participate in the regulation at cellular and humoral immunity, Th17 cells have been identified as a Th subpopulation that regulates inflammatory processes via production of distinct cytokines such as IL-17. The major feature of this subpopulation is involvement in protection against infection caused by microorganisms, and in the pathogenesis of autoimmune diseases and allergy. The role of Th17 cells and IL-17 in various stages of inflammatory process in rheumatoid joints remains poorly understood and still needs further studies. In this review, we summarize the latest discoveries about phenotype, differentiation and biological function of human Th17 cells, and also their role in the pathogenesis of rheumatoid arthritis.

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## Introduction

Rheumatoid arthritis (RA) is the commonest chronic, inflammatory, autoimmune disease characterized by symmetrical arthritis, destruction of articular cartilage and numerous organ damages. In its early stages the disease is characterized by pain and swelling, but not by deformity and damage. However, the disease remains active and uncontrolled inflammation causes deformity and instability of joints, because it is responsible for stimulating the destructive process in the joint. The inflamed synovial membrane contains several cell types, such as macrophages, monocytes, T cells, fibroblast, DC, plasma cells, which are involved in inflammatory and destructive processes. Joint damage in RA begins with the proliferation of fibroblast and the infiltration and accumulation of activated macrophages and T cells. The genetic associations of the HLA shared epitope alleles with developing of RA indicated that the disease is at least partially driven by T cells, which are important in driving the inflammatory process, and thus T cells could be targeted in clinical therapy.

In contrast to well-defined meaning of inflammatory mediators such as TNF-α in the pathogenesis of RA, a reference to T cells is not obvious and requires accurate knowledge [1]. T cells, which are the predominant cell type (constitute 30-50% of all types of cells) in the synovium of RA patients play a significant role in initiating and maintaining the inflammatory process. Naive Th cells differentiate into Th1, Th2, Th17 and regulatory T cell (Treg) subtypes according of their cytokine profiles and have different functional properties. Th1 cells principally secrete IL-2, IFN-γ and TGF-β and play an important role in the elimination of intracellular pathogen and tissue damage by the activation of macrophages or by the cytotoxic T cell. Moreover, Th1 cells enhance the induction of the complement system components, sensitized antibodies and antibodies involved in combating cytotoxic cells (e.g. IgG). However, Th2 cells produce IL-4, IL-5, IL-10, IL-13 and IL-25, promote the humoral and allergic response and play an import ant role in the elimination of extracellular pathogen [2-7].

Identification of cytokines IL-17 and IL-23 family in mediating the proliferation of the cells producing IL-17 revealed the existence of a third Th lymphocytes subpopulation identified as Th17 [8]. Similarly to the Th1 and Th2, Th17 cells require specific cytokines and transcription factors in differentiation. Distinct from Th1 and Th2 cells, Th17 are a typical proinflammatory cells, which promotes the induction of autoimmune tissue inflammation and play a key role in the development of autoimmune arthritis [6].

## IL-23 /Th17 axis

Th17 cells play a key role in autoimmune diseases through their participation in the maturation and differentiation of osteoblasts, and under the influence of IL-23 secrete IL-17A, IL-17F, IL-21, IL-22, IL-26 and GM-CSF [9,10]. In the ongoing inflammatory process in rheumatoid joint much more important is IL-23-IL-17 axis than IL-12-IFN-γ loop. The interactions between IL-17 and IL-23 is not only essential for the onset phase, but also for the destruction phase of RA characterized by the T cell-mediated activation of osteoclastogenesis [11,12]. In RA, IL-23 levels correlate with IL-17 levels in the joint fluid and with IL-17 and TNF-α level in the serum [13,14].

IL-17, which is a proinflammatory cytokine, have been originally cloned and described by Rouvier et al in 1993 [15], and named CTLA8 (cytotoxic T-lymphocyte-associated antigen-8), then subsequently renamed IL-17 and finally IL-17A [16]. IL-17 gene is located on the short arm of chromosome 6 in a position 6p12 and encodes a protein product of 155amino acids in length. Human IL-17A displays significant (62%) structural homology with mouse and rat IL-17A, both having remarkably conserved glycosylation sites [16]. IL-17 was the first discovered member of the IL-17 family. Another five members of the IL-17 family (IL-17B–F) have been discovered by large-scale sequencing of the human genome [17-19]. While IL-17E (IL-25) is produced mainly by Th2 cells, different cell types such as T cells, NK and neutrophils produce IL-17A and IL-17F. Moreover, IL-17A exhibits the highest level of expression on Th17 cells and became their "hallmark" [6]. IL-17 plays a role not only in the pathogenesis of autoimmune diseases, but also participates in the defence of the host organism during bacterial infections.

IL-23 was discovered as a member of the IL-6 / IL-12 superfamily, which belongs to the type I cytokines superfamily. This family contains

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34 type I cytokine receptors chains and 27 ligands, including those found in the mouse, in Drosophila and in Anopheles [21, 22] (Figure 1). IL-23 is a heterodimeric cytokine, which is composed of the p40 subunit in common with IL-12, and with a unique p19 subunit. IL-12 and IL-23 are secreted as disulfide-linked complex between the polypeptide namely p35 for IL-12 and p19 for IL-23, and a shared binding protein p40 [9]. IL-23 structure is a typical of class I receptor complexes. p19 subunit was originally cloned and described by Oppmann B et al [22]. Its gene is located on chromosome 12q13.2 and encodes a 189 amino acids sequence. The human p19 subunit is homologous with the amino acid sequence of murine p19 subunit in 70%. Functionally, IL-23 has been classified as a proinflammatory mediator responsible for keeping balance between effectors and regulatory T cell response and it is necessary factor for the development of T cell-dependent inflammation. IL-23 promote Th17 cells differentiation by inhibition of T-bet and Foxp3 expression. This cytokine together with IL-17A and IL-17F may play an important role in T cell-triggered inflammation by upregulating some of gene products involved in cell activation, proliferation and growth. In addition IL-23 it is an important inductor of various cytokines and chemokines that are crucial in regulating inflammatory response. Moreover, IL-23 can induce chronic inflammation through two independent pathways. A first pathway by the activation of Th17 cells and the second by the induction of the secretion of IL-17 by non T cells [9]. Defects in IL-23 gene or protein can be associated with decrease or increase immune suppression that could affect Th1, Th2 and Th17 cells and also innate immune response. Therefore, IL-23 probably in not essential for the development of human Th17 cells, but only appeared to be required for their survival and/or expansion [23-26].

## Human Th17 Cells Phenotype

The inflamed tissue, stimulated by immune and epithelial cells, can be the subject of different levels of certain chemokines expression that induce the recruitment of particular effector cells. Selective expression of chemokine receptors on the surface of each Th lymphocyte allows the determination of lineage cells and their effector functions, and the ability to move [27,28]. Evidence for the existence of Th17 cells in humans provide a number of studies indicating these cell surface markers. Human Th17 cells exhibited the expression of the transcriptional factor RORC2, as well as of the surface IL-23 receptor (IL-23R), and of the chemokine receptors, such as CCR4, CCR5 and CCR6 in absence of CXCR3, which is alternatively expressed by Th1 cells [29, 30]. Research conducted by Annunziato et al. [31] suggests a common origin Th1 and Th17. These authors observed that Th17 cell clones showed expression of β2 chain IL-12 and transcription factor T-bet that play a role in the differentiation of Th1 cells, under the influence of IL-23R and RORγt, respectively. Further studies [32-35] have also revealed the existence of certain differences in gene expression on the surface of Th17 clones compared with Th1 and Th2 clones. Lectin CD161 receptor, the human ortholog of murine NK1.1, proved to be one of the "up-regulated" genes in human Th17 clones, while the Th1 and Th2 clones were characterized by the absence of expression of this marker (CD161-) [34]. CD161 is expressed on themajority of NK cells and NKT cells, some T cells and thymocytes. Cells producing IL-17A was originally formed from CD161+CD4+ naïve T cell precursors, detectable in both peripheral blood and thymus, in response to increased activity of IL-1β and IL-23. However, the significance of the expression of CD161 marker on Th17 cells is still unclear. CD161 is capable to interact with a variety of ligands, including L-LT1 (lectin-like transcript 1) belonging to the family CLEC2 (C-type leptin domain family 2) and Pilar (Proliferation-induced lymphocyte-associated receptor). CLEC2 is selectively expressed in the skin, where Th17 cells move during the course of a chronic inflammatory process.

It is possible that via CD161 marker expression facilitate to Th17 cells transendothelial migration to inflamed tissue. In contrast, PILAR on the one hand by CD161 enhances the proliferation of T cells and induces the secretion of Th1 cytokine. On the other hand, due to clogging of the CD161 marker stimulates apoptosis in wild and early activated T cells [29,31,34]. Selective markers for human Th17 cells can be very helpful in understanding the pathogenic role of this cell subpopulation. Identification of a cells population exhibiting similar properties to the Th1 and Th17 allows exploring the phenomena of both the development and the functional relationship between Th1 and Th17 [36].

### Differentiation (DEVELOPMENT) Human Th17 Cells

Although the path of Th17 cells differentiation of naive CD4 + T cells is distinct from Th1 and Th2 cells, the Th17 cells development is also controlled by a combination of various cytokines and transcription factors. Th17 cell differentiation (Figure 1) occurs when naive CD4 + T cells encounter with antigen presenting cells (APCs, antigen-presenting cells) resulting in the production of certain cytokines in the lymphoid follicles. Studies conducted both in mice and humans showed that Th17 cells can be prepared not only by naive CD4 + T cells, but also by effector memory CD4 + T cells and CD4 + CD25 + Foxp3 T cells (Treg cells) [37]. Recent years brought huge growth of our knowledge on subject positive and/or negative regulators required for Th17 differentiation (Table 1), however her present state is not satisfied and contribution of individual cytokines, transcriptional regulatory events and epigenetic modification that control these process is still under discussion.

In particular, it seems to be difficult to compare the results of differentiation of human Th17 cells in in vitro experiments, due to the use of different naive-cell activation conditions or types of culture media [4]. While the mouse Th17 cells transformed with the naive T cell in the presence of IL-6 and TGF-β, and their phenotype is reinforced and / or stabilized by IL-23 and IL-21, many studies have not confirmed the involvement of TGF-β in the differentiation of human Th17 cells [38-41]. Acosta-Rodriguez et al. [38] observed that IL-1β in combination with IL-6 play a critical role in promoting the differentiation of naive CD4 + T cells into Th17 cells, while the addition of TGF-β inhibited this process. Chen [39] and Wilson [40] showed that naive T cells can be stimulated to differentiate into human Th17 cells in the presence of either IL-1β or IL-23, but not TGF-β. Studies by Van Beelen et al. [41] revealed that human Th17 cells are derived only from the memory cells, but not from the wild CD4 + T cell, and this effect was due to the oligomerization of nucleotides domain 2 ligand muramylopeptide, which enhances the production of IL-1 and IL-23 by dendritic cells. Study conducted by Evans et al. [37] showed that stimulation of human Th17 cells differentiation from circulating naive T cells occurs only through their contact with activated monocytes, while no soluble inducing factor has been identified. Recently, three independent research groups [42-44] demonstrated, in contrast to previous studies, that to the human Th17 cells development an appropriate TGF-β activity is required, such as in the mouse. Yang et al [42] confirmed that while IL-1β and IL-6 stimulates the secretion of IL-17 from human memory CD4 + T cells, TGF-β and IL-21 promotesnot only the differentiation of naive CD4 + cells towards human Th17,

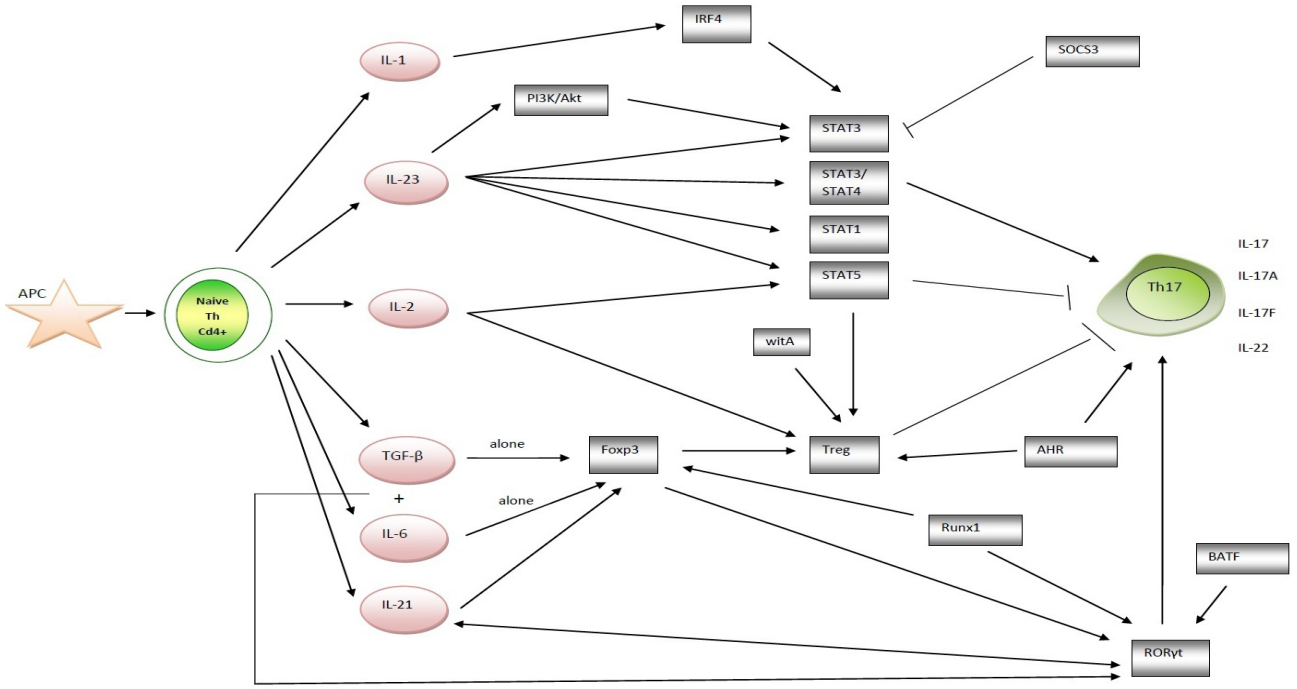


Figure 1: Signaling pathway in Th17 differentiation.
IL-23 through its receptors all STATs. STAT3/STAT4 alone and STAT3 through the RORγt enhances Th17 differentiation. STAT3 is inhibited by SOCS3. IL-2 through the STAT5 and Treg, and wit. A through Treg inhibits Th17 development. TGF-β acting together with IL-6 up-regulates RORγt and induces Th17 differentiation. TGF-β alone through the Foxp3 promotes the differentiation of Treg cells Treg cells and determines Th17 cell development. IL-6 and IL-21 alone inhibit Foxp3 expression and induces Th17 development. IL-21 also upregulates RORγt expression, which in turn induces more IL-21. IL-1 induces IRF3, which cooperates with STAT3 and promote Th17 development. STAT5 promotes Treg but inhibits Th17 development. Runx1 associates with both RORγt and Foxp3 and possibly regulates differentiation towards either the Treg or Th17 lineage. BATF is activated upon TCR stimulation and through cooperation with RORγt stimulates IL-17 gene transcription. AHR, on one hand promotes Th17-associated cytokines production, but on the other induces Foxp3Treg cells.

| Regulators | Function |
|---|---|
| **Positive** | |
| IL-1 | Control Th17 differentiation and proliferation. |
| IL-6 + TGF-β | Potent inducers of Th17 cells. |
| IL-21 | Induce IL-17 production; induce IL-23R expression, upregulates RORγt expression. |
| IL-23 | Development of T cell-dependent inflammation. |
| STAT3 | Binds promoters, enhancers and intragenic regions of many genes involved in Th17 development; binds and regulates IL-21, IL-21R and IL-23R genes; control expression of IRF4, RORγt and BATF. |
| RORC2 | "Master regulator" for Th17 development; promotes IL-17 expression; inhibition of Foxp3 gene transcriptional activity. |
| BATF | Regulates Th17-associated genes; controls RORC2 expression. |
| IRF4 | Regulates IL-17 and IL-21 production . |
| **Negative** | |
| IL-2 | Suppress TH17 differentiation in a STAT5-dependent manner. |
| IL-27 | Suppress Th17 development in a STAT1-dependent manner. |
| TGF-β | Through the Foxp3 promotes the differentiation of Treg cells. |
| STAT1 | |
| STAT4 | Negatively regulates IL-17 expression. |
| NF2F6 | Repression cytokine production in T cells, Suppress of the NFAT and AP-1 activity. |
| PPARγ | Inhibits T expression of Th17-associated genes. |
| Socs3 | Negative regulators of STAT3. |

Table 1. Positive and negative regulators of Th17 differentiation.

but also increase the level of transcription of mRNA of IL-17A and RORC. Manel et al [43] have shown that the combination of TGF-β, IL-1β and IL-6, IL-21 or IL-23 was necessary and sufficient to induce expression of IL-17 in naive human CD4 + T cells. TGF-β on the one hand, increases the expression of RORC agent, but on the other hand inhibits its ability to induce the expression of IL-17. Furthermore, Volpe et al [44] found that TGF-β, IL-1β, IL-6 and IL-23 are necessary for human Th17 development, but in different ways influence on the production of cytokines by Th17 cells. In addition, TGF-β deficiencies contribute to change the profile of Th17 cells to Th1. and IL-1β can be considered as two major factors inducing this mechanism. The process may also attend other mediators of inflammation what convinced by Boniface research group [45]. These authors demonstrated that prostaglandin E2 (PGE2) in a direct way promotes differentiation, expansion and pro-inflammatory functions of both murine and human Th17 cells. In humans, PGE2 increased expression of IL-23R and IL-1R, and together with IL-23 and IL-1β induced expression of transcription factors, cytokines and chemokines associated with Th17 cells.

In turn Cosmi et al. [34] showed that the cells that human IL-17A-producing cells could originate from CD161 + CD4 + T cells precursor present in both the thymus and in the peripheral blood, where under the influence of the joint action of IL-1β and IL 23 are activated. The presence of the IL-1β and IL 23 resulted in increased levels of expression of RORC2, IL-23R, T-bet, IL-12Rβ2, and increasing the number of subpopulations of Th1 cells. Despite the observed differences in the differentiation of human Th17 cells, IL-23

Regulation of Th17 development can also happen in a cytokine independent pathway. Other factors like vitamin A metabolite retinoic acid [46] induce expression Foxp3 and promote Treg differentiation and appear to inhibit Th17 development [38,45-47]. In contrast, sphingosine 1-phosphatase (S1P) induce development Th17 cell and inhibit Foxp3 expression [45,47]. Probably, another pathway that may play a significant role in Th17 development, differentiation and also proliferation are epigenetics modification of genes involved in this processes. However, in contrast to the signature of cytokine loci, relatively little is known about the epigenetic regulation of the regulators, which control Th17 differentiation.

## Transcription Factors Characteristic for Th17

The fact that Th17 cells develop regardless of transcription factors such as STAT1, STAT6, T-bet or GATA3, led to the discovery of the transcription factor RORC2 required to differentiate the different subpopulation of effector cells [49,50]. Human RORC2 (retinoic acid receptor-related orphan receptor C; shorter isoform gene RORC) is an ortholog of the mouse transcription factor RORγt. RORC2 belongs to the RORs family, which genes normally exists in several isoforms that differ in only the N terminal domain controlled of the genes expression by binding to specific sites on this genes promoter described as ROR-responsive elements (ROREs). Overexpression of RORC2 induced of the IL-17A, IL-17F, IL-26, TCR and CCR6 expression, initiates a wide range of phenotypic and functional programming during Th17 cells development, reduces levels of Foxp3 mRNA and proteins and reduces expression of granzyme A and B [4,43]. RORC2 may led to inhibition of Foxp3 gene transcriptional activity on the one hand by binding to two out of four ROREs on the Foxp3 promoter, and on the other hand by rivalry with NFAT about binding sites as that RORC2 have shown ability to binding to the NFAT- binding sites [51]. Knockdown of transcription factor RORC cause high Foxp3 levels and reduces expression of proinflammatory cytokines such as IL-1β, IL-6, IL-17, IFN-γ and TNF-α, suggesting that the role of RORC2 in Th17 cells differentiation involves not only in induction of Th17 characteristics genes, but also suppression of Treg cells specific programs [51]. Studies by Crome et al. [52] have demonstrated that RORC2 overexpression has only a small effect on the induction of IL-23R and CD161 molecules, although both of these surface markers are expressed on Th17 cells. These observations may suggest that RORC2 has no direct effect on the expression of Th17 cells surface molecules and alone is not sufficient to stimulate the production of IL-17A [42,49]. Probably other transcription factors in addition to RORC2 are required for fully activation of human Th17 cells. Among the transcription factors that may be involved in the differentiation of human Th17 cells, STAT3,IRF4, AHR, Runx1, BATF, SOCS3 and S1P are also mentioned [4,53]. STAT3, which activation is induced by IL-6, IL-21 and IL-23, beside of RORC2 is also a key transcriptional factor for Th17 cell differentiation. Mutations in the STAT3 gene significantly impair Th17 cell differentiation process and the secretion of cytokines specific for this subpopulation. Moreover, the deletion of SOCS3 (suppressor of cytokine signalling 3), that act as a negative regulator of STAT3 signalling pathway, increased the number of Th17 cells. The over-expression of the hyperactive form of STAT3 potentiated Th17 generation. IRF4 is a rare example transcriptional factor which is required for both Th2 and Th17 development, which deficiency of IRF4 impaired IL-17 production. This transcriptional factor on the one hand cooperate with STAT3 to induce RORγt expression, but on the other interact with NFATc1 and NFATc2 suggesting its effects on TH17 cells may be related to its effects on other Th subpopulation [53]. Recently though, it has been shown that BATF (AP-1 B-cell activating transcriptional factors) is essential for Th17 cell differentiation by binding to Th17-associated gene promoters and by maintaining RORC2 expression. Moreover, a total lack of BATF caused a complete loss of Th17 differentiation and limits the development of autoimmune diseases where Th17 cells play an indispensable pathogenic role [54]. The transcription factor AHR (aryl hydrocarbon receptor) is preferentially expressed by human Th17 cells, however, is still not known whether participates in their development [4]. All these transcriptional factors have relevant roles in determining lineage commitment through interaction with cytokine gene promoters and/or other lineage–specific transcriptional factors.

## Biological Functions of Human th17 Cells

Since increasing IL-17 concentrations were observed in autoimmune diseases, more and more attention has gained a precise definition of the role of human Th17 cells and their products in the process of ongoing immune response involved tissues [55]. Research has shown that these cells are much more effective in inducing inflammation than Th1 cells recognized so far for the "main culprit" of autoimmune diseases. Th17 cells are the dominant effector T cells involved in the induction of autoimmune chronic tissue by promoting the immune response. Th17 cells are also involved in the pathogenesis of allergic diseases by contributing to the activation and recruitment of neutrophils [56]. Association of IL-17 with human autoimmune disease was first presented in patients with rheumatoid arthritis, where higher frequency of Th17 cells had been found in the arthritic synovium [3]. Th17 cells produce cytokines, such as IL-17, IL-17F, IL-6, IL-21,IL-22 and TNF-a, which play an important role not only in the RA but also in the pathogenesis of experimental autoimmune encephalomyelitis (EAE) and collagen induced arthritis (CIA), and it induces DC to produce IL-12 and IFN-c in vitro [11,23,52,57-59].

Many studies on mice support these observations. IL-17, is also involved in the pathogenesis of EAE and absence of this cytokine protects from CIA [60-62], and two prototypical autoimmune mouse models, which are associated with deregulated Th1 responses [43]. Langrish et al. [8] demonstrated that clinical symptoms of EAE became severe in mice that received IL-23-driven Th17 cells but not in mice that received IL-12-driven Th1 cells. This observation suggests that Th17 cells are more efficient than Th1 cells for the induction of EAE and that IL-23-driven immune response in independent of the IFN-c-Th1 pathway. Moreover, in mice model, Th1 cells contribute to the inflammatory process rather than simply protecting tissue from Th17-driven inflammation. Similarly, increasing number of Th17 cells and IL-17 have also been observed in patients with inflammatory bowel disease, psoriasis, or multiple sclerosis [3,6]. However, in some tissues such as the intestine and perhaps liver, Th17 cells involved in the early phase of the acquired immunity may play a modulatory and/or protective role [10]. Two major cytokine secreted by Th17 cells - IL-17 and IL-22 - alone or in synergy stimulate a number of antimicrobial peptides such as β-defensin 2 or lipocalin 2 protein belonging to the S100 family [63]. The cytokines secreted by Th17 cells regulate the production of granulopoetic factors or matrix metalloproteinase leading to increased infiltration of neutrophils and other types of cells to the site of inflammation [24]. These cytokines also enhance the production of neutrophil chemokines CXCL1, CXCL8 and granulocyte activator CCL4 from eosinophils, and they can stimulate eosinophils to production of proinflammatory cytokines such as IL-1 and IL-6 helped neutrophil infiltration at the site of the target organ [9]. IL-17A and IL-17F may play an upstream role in T cell-triggered inflammation by upregulation some of the gene products involved in cell activation, proliferation, and growth [9]. IL-17 also induces the expression of the chemokine to the cells outside the immune system. IL-17 together with IL-23 are crucial factors in autoimmune inflammation to the CNS and it promotes inflammatory response such as upregulation of the matrix metalloproteinase MMP9, and increases angiogenesis but reduces CD8 T-cell infiltration. [64]. Human Th17 cells exhibited poor proliferative capacity and cytotoxic potential and probably they are less susceptible then Th1 or Th2 cells to the inhibition activity of Foxp3Treg clone. Annunziato et al. [65] described a new subset of T cell clones downregulated the expression of IL-17 and upregulated the production of IFN-c, termed Th17/Th1 cells, which has not been previously reported in mice. Th17 and Th17/Th1 cells are induced during Th17 cell differentiation of human T cells in vitro and they have shown not only expression of IL-23R, CCR6 and RORγt, but also that of T-bet, at both mRNA and protein level [56, 60, 65]. Interestingly, the IL-23 receptor did not play a role in the expansion of these cells, because they did not proliferate in response to IL-23 alone. Therefore, IL-23 probably in not essential for the development of human Th17 cells, but only appeared to be required for their survival and/or expansion [43,60,65,66]. Human Th17 and Th17 / Th1 clones shared some similarity properties, including ability to help B cell, low cytotoxic potential, reduced susceptibility to suppression by analogous CD4+Foxp3+ Treg cells [65]. It was also found that Th17 cells could promote the production of IgM, IgA, but not IgE, and that's way Th17 modulate B cells function and may actively recruit B cells to sites of inflammation [4,47].

Although Th17 cells are mainly connected with inflammatory and autoimmune diseases, various data evidence that this cells subpopulation take a part in response directed against extracellular and intracellular pathogens [63]. The role of Th17 cells in the defence of the host organism against pathogens was described in detail by using animal models. It has been shown that these cells are necessary for the immune system to protect against infections caused by bacteria Escherichia coli, Salmonella, Klebsiella pneumoniae and Bordetella pertussis. In humans, despite some reports, the knowledge on the role of Th17 cells in antibacterial defence is largely unknown [4].

Taken together, all these observations suggested that Th17 cells are the major player of autoimmune inflammation and may be a good therapeutic target for inflammation.

## Clinical Aspects and Aetiology of Rheumatoid Arthritis

RA is one of the commonest autoimmune disorders characterized by joint involvement leading to disability, deformity, morbidity and mortality [16,67]. RA can affect any joint, small and large, where cartilage overlies bone and with a joint cavity lined by synovial membrane that contains synovial fluid (SF) [67,68]. Early disease is characterized by pain and swelling, however, uncontrolled inflammatory processes may cause deformity and disability of joints [16,67]. Joint damage in RA begins with the proliferation of fibroblasts and the infiltration and accumulation of activated macrophages and T cells [65,69]. Interaction between synoviocytes and monocyte-macrophages cells leads to production of proinflammatory cytokines such as IL-1b and TNF-a, which are involved in the perpetuation of the chronic inflammation in RA [70,71]. RA is classified among systemic autoimmune disorders because of the presence of rheumatoid factor (RF) and other autoantibodies such as anti-cytrulline peptide (ACPA), which are present in serum and in the joints [16,72,73]. The sensitivity of RF is 60–85% in RA, however, in the first 3 months of disease, the RF is present in only 30% patients. Furthermore, ACPA appears to be rather sensitive (68%) and high specific (98%) for RA, which may be able to serve as an early diagnostic marker and prognostic factor of joint destruction [73,74].

Although, RA affects people all over the world, all races, even child (Juvenile Inflammatory Arthritis), some population demonstrate particularly low or high prevalence. However, irrespective of race, women are affected three times more than men and the peak age of onset being around the fourth and fifth decade of life [68,75]. The occurrence of RA is relatively constant in most European and North-American populations with prevalence between 0.5% and 1%. The highest occurrence of RA, with the prevalence between 5.3% and 6.8% has been shown in some American-Indian populations, such as Pima, Chippawa or Yakima. Moreover, the low occurrences of RA with the prevalence between 0.2% and 0.3% have been shown in populations from South Africa, Nigeria and South-east Asia [76]. The familial RA appears in about 10–30% of patients, in 12–15% of monozygotic twins, and in 3–4% of dizygotic twins [77].

RA is a disease of unknown aetiology, where environmental, immunological and genetic factors contribute to susceptibility and severity of the disease. Although, many studies have shown that alleles HLA-DR, which encode a special sequences (called shared epitope – SE), are very important genetic factors, but do not explain the total genetic background of the disease. Probably, in the pathogenesis of RA the other genes play a key role, which similarly as HLA gene take part in detecting bacterial and viruses' products [77, 78]. Interestingly, the majority of the identified genetic factors conferred risk to ACPA positive RA (PTPN22, C5/TRAF1, CTLA4, STAT4), whereas two genetic factors may be restricted to ACPA negative RA (HLA-DR3, IRF5) [79]. Recent studies have also shown that a number of proinflammatory and anti-inflammatory cytokine genes may

play a key role not only in the inflammatory process, bone and cartilagedestruction, but also may affect the course of RA. Genes IL-1b, TNF-a, IL-6, IL-10, IL-12 or IL-23 may serve as useful prognostic factors of RA, and, moreover, they are also associated with activities of enzymes in SF, which play a role in bone degradation [80].

## The Role of Human Th17 Cells in RA Pathogenesis

Initial evidence for a pathogenic role of Th17 cells in RA come from research conducted by a team of Miossec et al [81]. They and other research groups have demonstrated that IL-17 level increases in the sera and synovial fluid of RA patients, and that this cytokine is present in the T cells-rich areas of the synovium [81-83]. Although Th17 cells are presented in both synovial membrane and the blood mononuclear cells of patients with RA, their levels showed no significant differences compared to the healthy volunteers [51]. The study by Shahrara et al [26] has shown that the frequency of Th17 cells is higher in synovial fluid of RA patients than in blood of healthy volunteers. The differences between these studies are not entirely clear and may be explained by different selection of patients, the type of the treatment or technical differences. IL-17 plays a role not only in the early stages of RA, but also later, during disease progression (Figure 2) and it was detected at both the mRNA and protein level in RA synovium. Increased level of IL-17 and TNF-α mRNA expression in the synovium of RA patients are predictive of more severe joint destruction, whereas high levels of IFN-γ mRNA in the joint have a protective function [46]. The IL-17 receptor expressed and initiates an inflammatory response in a number of different cell types playing a key role in the pathogenesis of RA, including monocytes, macrophages, fibroblasts, chondrocytes and osteoblasts. IL-17 by interacting with its receptor stimulates these cells for the production of several proinflammatory cytokines such as IL-1β, IL-6, IL-23, TNF-α promoting inflammation and the development of Th17 cells. In this way, Th17 cells present in the joint may create a positive feedback loop leading to the continuous activation of T cells, which is a critical event in the generation of autoimmunity [46].

Studies conducted by the Koshy et al. [66] have shown that IL-17 alone and synergistically in combination with other proinflammatory cytokines can induce chondrocyte-mediated cartilage collagen breakdown. Similar results were presented by Chabaud et al [90] have shown that IL-17 can induce cartilage proteoglycan degradation in vivo and ex vivo, as well as its synthesis ex vivo.IL-17 stimulates the expression of cyclooxygenase-2 (COX-2) in synoviocytes and mediates the induction of IL-6 and IL-8 playing a role in the ongoing inflammatory process in the synovial fluid and activated synoviocytes type B via a path-dependent kinase 3 fosfatydylinositosol/ Akt and NF-κB [52]. Furthermore, Koenders et al [88] observed in their study that neutralization or blocking IL-17 during reactivation of antigen-induced arthritis reduces joint swelling, joint inflammation and bone erosions.. IL-17 inducing IL-23 production by synovial fibroblast results in a positive feedback mechanism which perpetuates synovial inflammation in RA. IL-23p19-IL-17 axis plays a pivotal role not only in the initial, but also in the destructive phase of autoimmune arthritis and therefore distorts the way IL-23/IL-17 may be a potential target in the treatment of RA [12]. Moreover, the role of Th17 cells in various stages of inflammatory process in rheumatoid

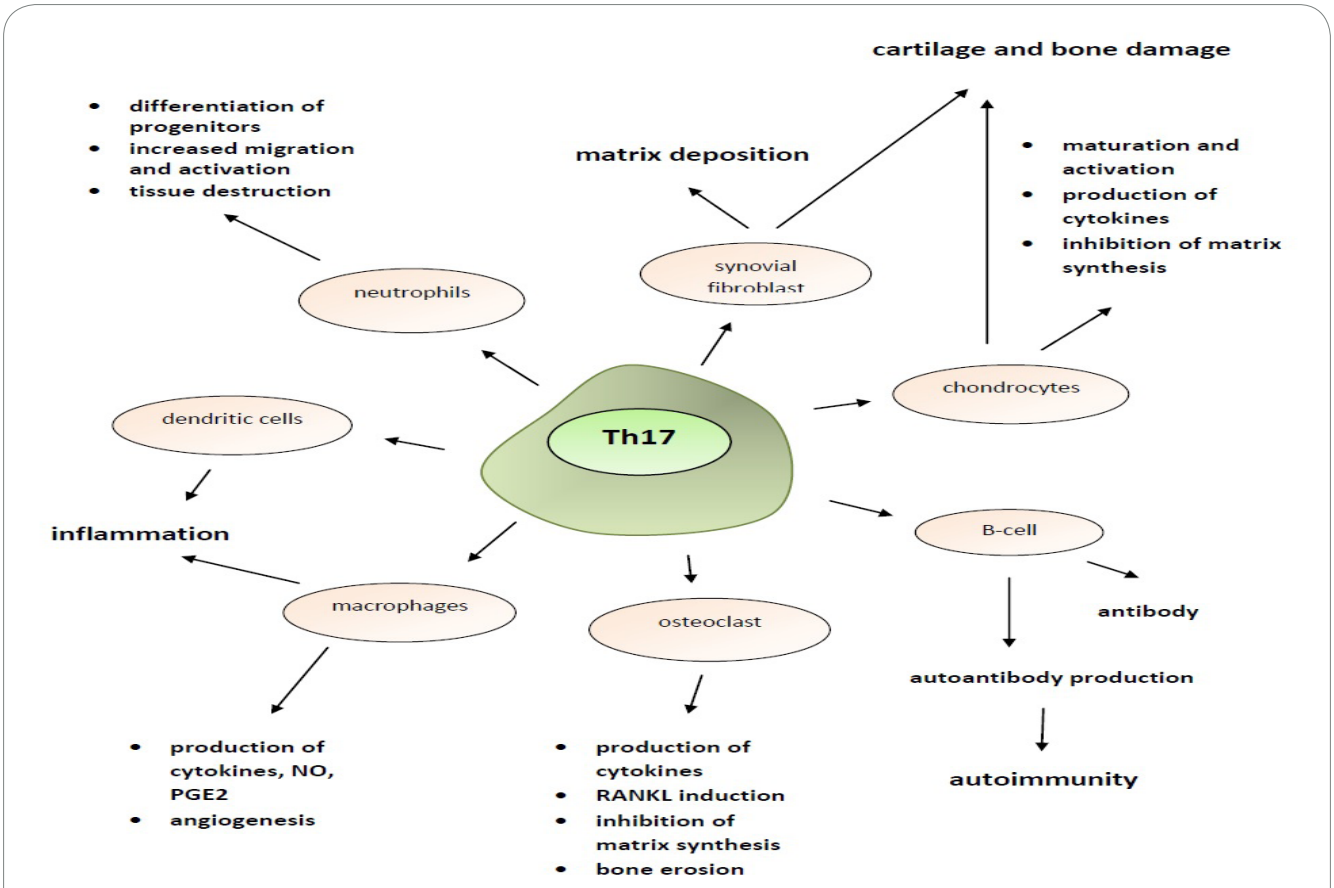


Figure 2: Role of Th17 cell in the pathogenesis of rheumatoid arthritis.

joints remains poorly understood and still needs further studies.

In patients with RA, Th17 play a crucial role in inducing and perpetuating the chronic inflammation and cartilage damage. Th17 stimulated by the IL-23 promotes osteoclastogenesis inducing RANKL on mesenchymal cells and in cultures of osteoblast. RANKL is not only involved in regulating of osteoclastogenesis, but also as a key factor in the bone erosion process and stimulates synovial fibroblasts, endothelial and epithelial cells to produce IL-6, IL-8 and PGE2 [2]. Chen et al. [84], Nakae et al. [85] and Kotake [86] have shown that IL-23 and IL-17 can stimulate osteoclast formation in two independent pathways -first, by the direct acting on myeloid precursors inducing receptor activator of NF-kappa B expression (RANK), and second by indirectly upregulating RANKL expression in osteoblast. Moreover Th17 cells stimulate the activity of matrix metalloproteinase, matrix catabolism and bone resorption [16,37,87].

## Summary

While there are still many unknowns relating to the phenotype, function and differentiation of human Th17 cells, it is clear that IL-17 and other cytokines associated with Th17 cells play an important role in the pathogenesis of autoimmune diseases [4]. Knowing the exact operation and the development process described cells require a number of researches to define the interaction of human cells, not only Th17 cells belonging to the immune system cells but also outside the system. Understanding the regulatory path of human Th17 cells is necessary for the understanding of the pathophysiology of RA, improvements to existing and development of new, perhaps more personalized and more effective treatment methods.

## Competing Interests

All authors state that they have no conflict of interest related to this work.

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## Author Contributions

Both the author contributed equally study conception and design, acquisition of data, analysis and interpretation of data, drafting of manuscript.

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