

Autoimmune diseases in the TH17 era

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A new subtype of CD4⁺ T lymphocytes characterized by the production of interleukin 17, i.e., TH17 cells, has been recently described. This novel T cell subset is distinct from type 1 and type 2 T helper cells. The major feature of this subpopulation is to generate significant amounts of pro-inflammatory cytokines, therefore appearing to be critically involved in protection against infection caused by extracellular microorganisms, and in the pathogenesis of autoimmune diseases and allergy. The dynamic balance among subsets of T cells is important for the modulation of several steps of the immune response. Disturbances in this balance may cause a shift from normal immunologic physiology to the development of immune-mediated disorders. In autoimmune diseases, the fine balance between the proportion and degree of activation of the various T lymphocyte subsets can contribute to persistent undesirable inflammatory responses and tissue replacement by fibrosis. This review highlights the importance of TH17 cells in this process by providing an update on the biology of these cells and focusing on their biology and differentiation processes in the context of immune-mediated chronic inflammatory diseases.

Key words: Autoimmune diseases; Cytokines; TH17 cells; IL-17; IL-22; IL-23

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Introduction

Early studies by Mosmann et al. (1) have demonstrated that CD4⁺ T cells could polarize into two different subsets, T helper 1 (Th1) and T helper 2 (Th2), based on the profile of the cytokines secreted (1). Later on, several investigators highlighted the existence of a neutral subset, Th0, able to produce either Th1 or Th2 cytokines. It is becoming increasingly clear that antigenic stimulation and the peculiar intrinsic characteristics of the milieu induce naive T cells to proliferate and differentiate into different effector T cell subsets with specific features such as cytokine production and functional properties (2).

Th1 cells are mainly characterized by the production of large quantities of interferon-gamma (IFN- γ), while Th2 cells secrete interleukin (IL)-4, IL-5, and IL-13. Th1 cells are the main agents in delayed type hypersensitivity immune response through activation of macrophages, and

are crucial to host defense against intracellular pathogens. In contrast, Th2 cells are more efficient in mounting humoral immune responses, triggering the production of antibodies and promoting eosinophil infiltration. Th2 responses are important to limit extracellular pathogens and can also counterbalance Th1 immune responses. Th0 cells can differentiate into Th1 or Th2 subsets at very early stages of cell activation. Since Th1 cells are fully capable of secreting cytokines, they can in turn inhibit Th2 cell differentiation and vice versa. Several regulatory molecules are involved in this process, such as cytokines, cytokine receptors and transcription factors, ultimately leading to epigenetic modifications in the target T cells (Figure 1).

The control of immune responses is important for proper functioning of the immune system and necessary to avoid immunopathology, largely manifesting as allergic and autoimmune diseases. In human autoimmunity, the Th1 immune responses have been traditionally associated with

the induction and progression of disease. However, this paradigm has been recently challenged following the observation in mouse models that the absence of IFN- γ signaling does not constitute resistance to the development of autoimmunity; on the contrary, these animals are even more susceptible to these diseases. These observations have called the interplay of Th1 cells and autoimmune diseases into question, pointing to the possible existence of additional T cell subtypes, which differ from the Th1 subpopulation and are able to induce and perpetuate local inflammation and autoimmunity.

TH17: An overview

The initial studies on TH17 cells have involved reports on *Borrelia burgdorferi* infection in animal models. Stimulation with sonicates and synthetic antigens of the bacteria

induced IL-17 production by T cells, independently of the production of Th1 and Th2 cytokines. The same pattern of IL-17 secretion was induced by the BCG strain of *Mycobacterium bovis* (3). Further evidence that led to the discovery of this cell population came from studies in autoimmune murine models, namely rheumatoid arthritis (RA) and multiple sclerosis models (MS) (4,5). The cumulative evidence about the existence of a distinct subset of T cells characterized by the secretion of large amounts of IL-17 has led to the proposal of a third lineage of Th cells designated TH17 cells (6,7).

IL-17 (also known as IL17A) and IL-17F cytokines are members of the IL17 family, which encompasses potent inducers of inflammation, promoting cellular infiltration and the production of several pro-inflammatory cytokines and chemokines. IL-17 binds to and signals through IL17 receptor A (IL-17RA), a member of the IL17R family that is

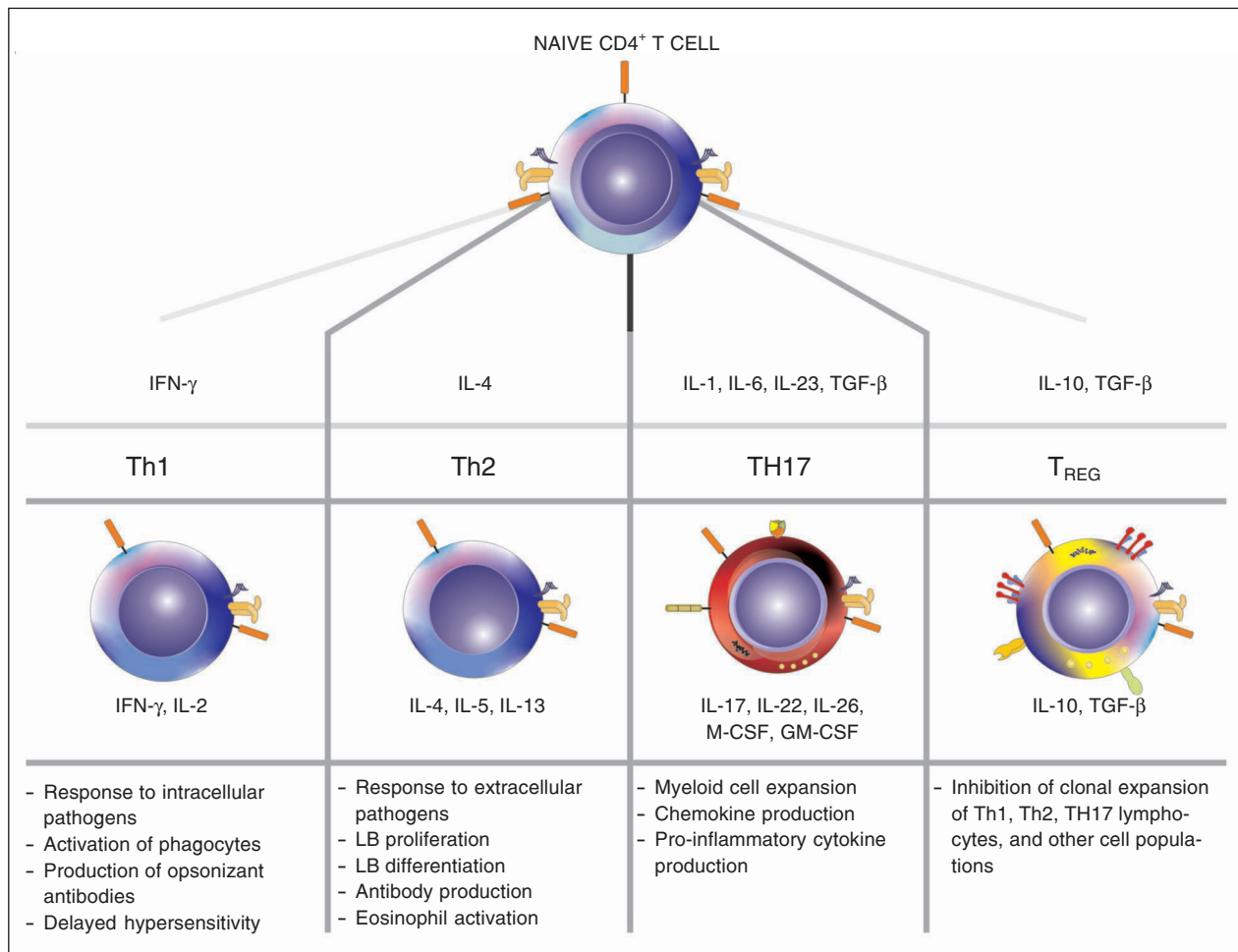


Figure 1. Schematic representation of naive CD4 T cells under different stimuli and possible differentiation pathways. IFN- γ = interferon gamma; IL = interleukin; TGF- β = transforming growth factor beta; Th1, Th2 = T helper cells 1 and 2; T_{REG} = regulatory T cells; M-CSF and GM-CSF = macrophage and granulocyte-macrophage colony-stimulating factor; LB = B lymphocytes.

largely expressed by epithelial cells and mesenchymal cells such as endothelial cells and fibroblasts. The genes that encode IL-17 and IL-17F are located on the same chromosome in both mice and humans. The majority of studies on the subject have focused on IL-17 or IL-17A. It is known that IL-17F has pro-inflammatory characteristics similar to those of IL-17, albeit with weaker activity than the homologous IL-17A. Some studies in humans have proposed a possible function of IL-17F in the physiopathology of human asthma. The present review will focus mainly on IL-17 since it is the major cytokine produced by TH17 cells, but the IL-17 family members also comprise IL-17B, IL-17C, IL-17D, and IL-17E (also known as IL-25) secreted by a large number of cells (8).

With the discovery of TH17 cells, many questions about the physiopathology of certain chronic inflammatory diseases can now be better understood, since the mechanism of such immune responses did not fit under the Th1 or Th2 paradigm. The neutralization of IL-17, without interfering with the Th1 effective pathway, is capable of offering full recovery from some murine autoimmune diseases, such as collagen-induced arthritis (CIA) and experimental autoimmune encephalitis (EAE) (5,9). The effectiveness of such an approach could be achieved when the treatment is administered during priming or even when the disease is already established (5,9). Recently, other studies have associated the participation of TH17 cells in the pathophysiology of several human inflammatory diseases, including viral hepatitis (10), asthma (11,12) and transplant rejection (13).

The discovery of IL-23 shed light on the differentiation route of this novel T cell phenotype. This cytokine is a dimer composed of the subunits IL-12p40 and IL-23p19. While the IL-12p40 subunit is a common chain for IL-12 and IL-23, the IL-23p19 and IL-12p35 subunits are exclusive of IL-23 and IL-12, respectively. Mild autoimmune manifestations have been observed in mice susceptible to autoimmunity when knocked out for IL-12p40. In contrast, in IL-12p35 receptor knockout animals, the development of autoimmunity occurred normally. Taken together, these studies indicate that IL-23, but not IL-12, is a crucial element in promoting autoimmunity. The human counterpart of these findings comes from the observation that antibodies against the IL-12p40 subunit were effective in the treatment of Crohn's disease (14) and showed good results in clinical trials with patients with MS and psoriasis (15,16).

Although IL-23 is fundamental for survival and for terminal differentiation of TH17 cells, its exact function in the induction of these cells has yet to be fully understood. This is partly due to the absence of the IL-23 receptor in the

naive T cells, and its expression only in activated cells. Thus, only previously activated or memory T cells become susceptible to the action of IL-23 and as such, amenable to differentiate into TH17 cells (17). Different alternative factors of differentiation for TH17 cells have been identified. Three independent studies directly addressed this issue by reporting TGF- β and IL-6 as the main cytokines able to induce the differentiation of naive T cells into TH17 lymphocytes (18-20). Sutton et al. (21) also reported on the importance of IL-1 and IL-23 as differentiation factors and as survival promoters in murine studies. Evans et al. (22) reported that the induction of TH17 cells is mediated by cell-cell contact with Toll-like receptor-activated monocytes in the context of T cell receptor ligation.

A recent study has added further complexity to the understanding of the TH17 induction pathway and its function. In a mouse model, McGeachy et al. (23) showed that TH17 cells produce IL-17 in the presence of IL-6 and TGF- β , but they do not have pathogenic potential *in vivo*, even with a high production of IL-17. Apparently, this *in vivo* behavior was due to their capacity to also produce IL-10 that has modulatory effects on the action of IL-17. However, TH17 cells stimulated in the presence of IL-23 also promoted the expression of pro-inflammatory IL-17 and chemokines, but did not produce IL-10. Thus, it seems that IL-6 and TGF- β initiate the polarization towards TH17 cells, but these cells would be devoid of pathogenic potential *in vivo* unless there was the participation of IL-23 capable of providing immune inflammatory capacity to TH17 cells (23).

Several other cytokines may interfere with the development and proliferation of TH17 cells. The neutralization of Th1 and Th2 cytokines, such as IFN- γ and IL-4, increases the number of IL-17-producing cells generated by stimulation with IL-23 (24). More recently, it was demonstrated that IL-27, IL-25, and IL-13 have inhibitory functions on TH17 development. The absence of these cytokines exacerbates inflammatory processes and increases the number of TH17 cells in an inflammatory milieu (9,25). Akin to what has been previously observed for Th1 and Th2 cell polarization, the presence of co-stimulatory molecules such as CD80, CD86, OX40, and ICOS is fundamental for TH17 differentiation in the presence of IL-23 (24).

As mentioned earlier, TH17 cells have an important function in protecting against infection by extracellular microorganisms due to their ability to secrete pro-inflammatory effector cytokines such as IL-21, IL-22, and IL-26, as well as smaller quantities of IL-6 and TNF- α (Figure 2).

The continuous balance among T cell subsets during the course of pathology is of primordial importance to define the outcome of the disease. Specific transcription

factors regulate the commitment and the stability of these T cell subsets. T-bet is involved in the polarization of Th1-specific T cells, while GATA-3 is related to Th2 differentiation, and the transcription factor Foxp3 is important for regulatory T cell commitment. Recently, two transcription factor members of the retinoic acid receptor-related orphan (ROR) nuclear hormone receptor family were shown to regulate the differentiation of TH17 cells. The first to be described was ROR γ , which is encoded by the RORC gene and is best represented by the isoform ROR γ t, which is exclusively expressed in cells of the immune system. This transcription factor is induced by TGF- β and IL-6, and the overexpression of ROR γ t polarizes Th0 cells into the TH17 lineage and blocks the Th1 and Th2 pathways. The knockout of ROR γ t in Th0 cells inhibits IL-17 and IL-17F expression in response to TGF- β and IL-6 or IL-21, and restrains TH17 differentiation. Recently, it was reported that ROR α was also expressed by TH17 cells and induced by TGF- β and IL-6. This transcription factor has properties similar to those of its homologue and could inhibit Th1 and Th2 differentiation. Interestingly, ROR α deficiency in T cells results in a selective decrease in IL-17 and IL-23R expression, but has only a mild inhibitory effect on EAE induction, while the deficiency of its counterpart (ROR γ t)

results in attenuated autoimmune development in the EAE model (26). In summary, ROR γ t and ROR α have a synergistic effect on TH17 differentiation, while *in vivo* they are induced at the same time in an inflammatory milieu, but with some differences in regulating biological functions of TH17 cells depending on the disease model.

TH17 cells in animal models of autoimmune diseases

Although the first evidence of IL-17-producing cells came from studies of a murine model of infectious diseases, the greatest advances in understanding the immune functions of these cells were based on data on murine models of autoimmunity. IL-17 is directly involved in the pathophysiology of experimental arthritis. In the absence of IL-17, these mouse models developed mild articular disease (4). In the CIA model, rats treated with an antagonist of the IL-17 receptor (IL-17R) had significantly reduced manifestations (27). Treatment with anti-IL-17 monoclonal antibodies led to an improvement in articular destruction in mice with CIA (28). In EAE, the deficiency of IL-17 or the use of IL-17-blocking antibodies prevented the development of the disease or diminished its severity (5).

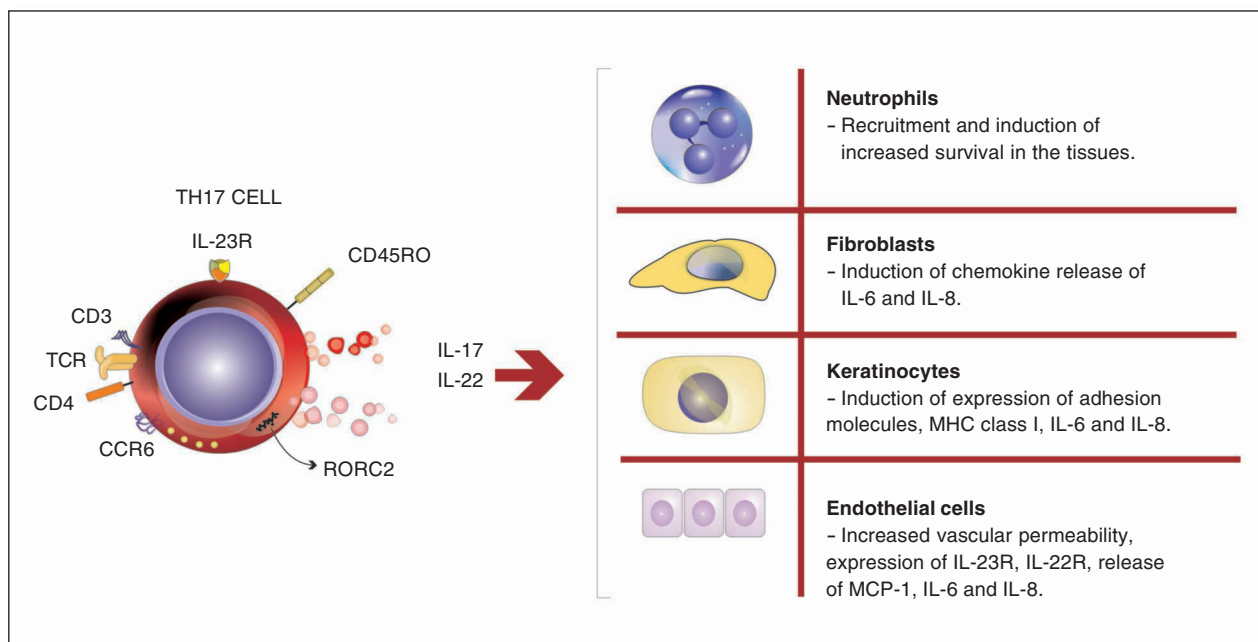


Figure 2. TH17 lymphocytes are critically involved in activating and maintaining the inflammatory response against microorganisms on the basis of their capacity to produce inflammatory mediators and characteristic migration to inflamed sites. The figure represents some cells susceptible to the action of IL-17 and IL-22 with their respective effects on target cells. TCR = T cell antigen receptor; ROR = retinoic acid receptor-related orphan; IL = interleukin; CCR = chemokine (C-C motif) receptor; MHC = major histocompatibility complex; MCP-1 = monocyte chemoattractant protein-1.

In the last 3 years, many studies have demonstrated the importance of TH17 cells in the pathogenesis of autoimmune inflammatory diseases, basically showing its pathogenic function. In a more recent study, it was shown that IL-17 also contributes to the formation of lymph node germinal centers and to the production of autoantibodies in mice with lupus-like disease (29). In murine models of colitis, significant reduction in the migration of neutrophils to the colon and reduced amounts of CXC chemokines were achieved in IL-17R knockout mice, or by blocking IL-17R using IL-17R-Ig fusion protein, thereby demonstrating the critical role of IL-17 and IL-17R signaling in gut inflammation (30). The blockage of IL-23 was effective in preventing colitis by inhibiting IL-17 and IL-6 production in IL-10-deficient mice (31). Finally, another study of a colitis model showed that IL-23 acts as an effector cytokine within the innate intestinal immune system by inducing intestinal inflammation in response to activation through CD40. The treatment with anti-IL-23 was able to prevent IL-17 production and development of colitis independently of the action of T cells, since the disease was reproduced in T cell-deficient mice. All of these data suggested the possible contribution of other cells, such as non-conventional lymphocytes, as a source of IL-17 (11).

Distinctive characteristics of human TH17 cells

The current concepts on the differentiation of TH17 cells have been drawn from murine models. Given the importance of the cytokine members of the IL-17 family in the pathogenesis of some human diseases, it is of fundamental importance to understand how this family is expressed in human T cells, especially in conditions that could make a human naive T cell differentiate into a TH17 cell subset. The initial studies evaluating the induction of IL-17 production by human lymphocytes showed that this differentiation pathway is dependent on activation signaling through the T cell antigen receptor in the presence of appropriate co-stimulation, associated with the presence of IL-23 (32). However, these studies have not taken into consideration the stage of maturation of these cells, i.e., whether they were naive or memory cells.

An interesting aspect of human T helper cells is their great plasticity for differentiation compared with their murine counterparts. IL-17-producing T cells are promptly identified in populations of memory CD4⁺ T lymphocytes in humans although their commitment to the TH17 specific lineage is less clear since in humans these cells produce both IL-17 and IFN- γ . In addition, unlike the TH17 murine cells that are easily induced by the combination of TGF- β

and IL-6 cytokines, this combination is completely inefficient in generating human TH17 cells. On the other hand, some studies in humans have shown that IL-23, in the presence of IL-1, is effective in promoting the production of IL-17 by T lymphocytes (33), probably by the concomitant action of TGF- β present in the bovine fetal serum of the medium used in the experiments.

Two recent studies evaluating naive T cells from human umbilical cord showed that the presence of TGF- β is essential to induce the ROR γ t transcription factor, and in the presence of IL-23 and IL-1, combined with inflammatory cytokines such as IL-6, IL-21 and TNF- α , they acquired the capacity to produce IL-17 at optimal levels. These cells could also produce several other inflammatory cytokines such as IL-21, IL-22, IL-6, TNF- α , and IFN- γ . The cytokine profile produced by human TH17 cells seems to be also influenced by other mediators present in the culture (34-36).

There are several studies of human diseases suggesting an important role for IL-17 in the pathogenesis of human inflammatory and autoimmune diseases. IL-17 is involved in the inflammatory response observed in exacerbation episodes of IgA nephropathy by stimulating the release of pro-inflammatory cytokines from peripheral blood monocytes (37). In human renal biopsy samples, scattered IL-17 antigen was found in borderline acute renal rejection and could be used as a predictive parameter for subclinical renal allograft rejection in the future (13).

TH17 has been implicated in host defense against a number of microorganisms. IL-17 promotes expansion and recruitment of innate immune cells such as neutrophils, and also cooperates with TLR ligands, IL-1 β , and TNF- α to enhance inflammatory reactions. It also stimulates the production of β -defensins and other antimicrobial peptides. Its receptor, IL-17RA, is ubiquitously expressed and shares many features with classical innate immune receptors. Their intracellular tail motif signaling converges to a common inflammatory transcription pathway (38).

Full comprehension of the mechanisms of polarization of T helper lymphocytes in humans is essential to gain a better understanding of the physiopathological mechanisms of diseases and for the development of future approaches to their treatment.

TH17 cells in human autoimmune diseases

Some of the TH17 cell products are found at higher levels in affected tissues in human diseases and in their respective animal models (Table 1). The essential function of this T cell subset in the induction and development of murine autoimmune diseases has been confirmed and its

Table 1. Role of TH17 in human diseases and mouse models.

Disease	TH17 related cytokines			References	
	IL-17	IL-21	IL-22	Mouse	Human
Rheumatoid arthritis	Pathogenic	Pathogenic	ND	4,27,28	43,39-45
Multiple sclerosis	Pathogenic	Pathogenic	ND	5,33	51,52
Systemic lupus erythematosus	Pathogenic?	Pathogenic	ND	29	48
Systemic sclerosis	Pathogenic	ND	Pathogenic	24	53
Inflammatory bowel disease	Protective (acute) Pathogenic (chronic)	ND	ND	11,30,31	54
Ankylosing spondylitis	Pathogenic?	ND	ND	None	55
Hepatitis	None	ND	Protective	10	None
Asthma	Protective (effector) Pathogenic (priming)	Protective	ND	11,12	8
Contact hypersensitivity	Pathogenic	ND	ND	None	59
Psoriasis	Pathogenic	ND	Pathogenic	None	36,50,55
Kidney transplant	Pathogenic	ND	ND	13	13

ND = not determined.

actual role in human autoimmune diseases is now supported by a body of favorable evidence.

Studies on the participation of TH17 cells in RA have redirected the focus of attention, hitherto limited only to Th1 cells. The products of TH17 cells, such as IL-17 and IL-23, are present in the serum, synovial fluid and synovial tissue of the majority of patients with RA, while they are absent in osteoarthritis (39-41). Under normal conditions, IL-17 is undetectable or detected at very low levels in the serum of healthy controls. However, high levels of this cytokine were detected in serum and synovial fluid in two studies evaluating patients with RA (40,42). IL-17-producing clones were recoverable from effector T cells of synovial tissue of patients with RA (43).

Peripheral blood T cells from patients with RA, co-incubated with synovial fibroblasts in the presence of type II collagen, induced the production of IL-15, TNF- α , and IL-18 by the synovial cells. In turn, T cells produced high levels of IL-17 and IFN- γ in response to these cytokines (40).

IL-17 also stimulates an increased production of IL-6, promotes cartilage destruction, inhibits the synthesis of collagen, and induces bone re-absorption in patients with RA (44,45). Synovial fibroblasts from RA patients treated *in vitro* with IL-17 produce IL-6 and IL-8 and increase gene expression for chemokines and metalloproteinases. These cells participate in the perpetuation of joint inflammation as dynamic partners in a mutual activation feedback via secretion of cytokines and chemokines that stimulate each other (24). Patients in the initial stages of inflammatory arthritis progressing to the development of RA have a distinct transitional profile of cytokines characterized by

the production of IL-2, IL-4, IL-13, IL-17, and IL-15 in synovial fluid. Interestingly, this Th2/TH17 cytokine profile can no longer be observed at later stages of the disease (46). A recent 2-year prospective study also reported the same behavior of cytokine profile at the beginning of the disease (47). These studies support the idea that T cells play a distinct role in the early stages of the disease, emphasizing the action of IL-17 and other cytokines not directly linked to TH17 cells. This initial response differs from that occurring in late stages of disease, which are characterized by a predominantly Th1-driven inflammatory response. It is worth emphasizing that in the cited study the authors described a positive correlation of mRNA levels of the cytokines produced by TH17 cells, such as IL-1, TNF- α and IL-17, with progression of articular damage.

Other studies on different autoimmune diseases such as systemic lupus erythematosus (48), psoriasis (36,49,50), multiple sclerosis (51,52), systemic sclerosis (53), bowel inflammatory disease (54), ankylosing spondylitis (55), and juvenile idiopathic arthritis (56) have demonstrated the presence of high levels of IL-17 and other cytokines related to its pathway in serum and tissues.

Patients with bowel inflammatory disease have high expression of IL-17 mRNA and protein at the intracellular level in intestinal mucosa compared to normal controls or patients with infectious or ischemic disease (54). Annunziato et al. (17) demonstrated the presence of CCR6⁺ IL-23R⁺ IL-17-producing cells and/or polyfunctional IL-17/IFN- γ -producing cells in the intestine of patients with Crohn's disease. In the same study, higher serum levels of IL-17 correlated with disease exacerbation (17).

High levels of IL-17 were detected in the skin of patients with psoriasis and this cytokine was able to induce the expression of adhesion molecules and pro-inflammatory cytokines in human keratinocytes (49). Liang et al. (50) showed that IL-22 was also found at high levels in the skin of patients with psoriasis and contributed, in synergy with IL-17, to the induction of proteins associated with the cellular processes of differentiation and proliferation in this disease (50). In another study, Wilson et al. (36) demonstrated that some cells from the skin of patients with psoriasis expressed IL-23R, IL-17A, IL-17F, IL-26, CCL20, and the ROR γ t transcription factor, suggesting the presence of TH17 in the skin of these patients. This study also showed that IL-1 and IL-23 are important for the differentiation of these cells (36).

In a recent study, Kebir et al. (51) reported on the expression of receptors for IL-17 and IL-22 at the blood-brain barrier level of MS lesions and demonstrated that IL-17 and IL-22 contributed *in vitro* to the changes in the blood-brain barrier architecture. In addition, *in vitro* studies with human cells showed that TH17 lymphocytes can efficiently cross this barrier and kill neurons by the release of granzyme B, promoting inflammation of the central nervous system and infiltration of further inflammatory cells (51). Tzartos et al. (52) found high levels of IL-17 mRNA (*in situ* hybridization) and protein (immunohistochemistry) in lymphocytes, astrocytes, and oligodendrocytes located in areas of active injury to the central nervous system in patients with MS. They also observed a higher frequency of CD4⁺IL-17⁺ and CD8⁺IL-17⁺ T lymphocytes in areas of active lesion (73%) compared to inactive lesions (17%) of the brain. These observations suggest that both CD4⁺ cells and CD8⁺ IL-17-producing T cells play an important role in MS pathophysiology (52). Figure 3 depicts a schematic view of the possible participation of TH17 cells in the pathophysiology of MS.

Many of the molecules currently being focused on for therapeutic targeting in the treatment of autoimmune diseases are directly or indirectly associated with the TH17 axis. Particularly noteworthy are IL-17 and GM-CSF, soluble mediators of inflammation targeted in clinical studies and even for immunobiological use in clinical practice such as TNF- α , IL-6 and IL-1 blockers that could be a product or an inducer factor for TH17 subset development. Phase I clinical studies with antibodies against the IL-12p40 subunit (a common chain of the IL-12 and IL-23 receptor) in patients with psoriasis and MS have shown good "tolerance" and positive response, yielding improvements in clinical and laboratory parameters (15,16). A multicenter phase II study with an anti-IL-17 monoclonal antibody (AIN45-7) is currently underway in patients with Crohn's disease and psoria-

sis resistant to conventional therapies. These trials will help to better understand the relevance of TH17 cells in the pathogenesis of these diseases and to evaluate whether anti-IL-17 therapy will result in greater efficiency and safety benefits over conventional treatment strategies.

Final considerations

High levels of IL-17 and other inflammatory mediators of the TH17 pathway have been observed in several human autoimmune disorders and in related animal models. However, these results must be interpreted with caution. It is important to identify the cellular source of IL-17 and related cytokines in humans. Despite the focus on IL-17-producing CD4⁺ T cells, other lymphocyte subsets might have similar capacity, such as NKT cells, $\gamma\delta$ T lymphocytes and CD8⁺ T lymphocytes, all with the capacity to produce IL-17 under certain circumstances (57-59).

Although the necessary conditions for induction of naive T cells producing IL-17 may seem clear, the memory T cells are the major source of this cytokine in humans. For this latter T cell population, the presence of IL-23 is not necessary for induction of IL-17 since a regular T cell antigen receptor stimulus and appropriate activation of co-stimulating molecules seem to suffice. In contrast to observations in mice, human TH17 cells also produce IFN- γ , and are thus considered to be "double positive". Perhaps because of the novelty of this new subset of T lymphocytes, no specific phenotypic surface marker for TH17 has yet been identified. At this time, the expression of the receptor for IL-23 and the chemokine receptor CCR6 has been used to purify IL-17⁻IFN- γ ⁺ T cells (34,36). Despite the advances made to date by studies in murine TH17 cells, human CD4⁺ T cells seem to behave with a much greater plasticity and are thus less "terminally differentiated".

Further research on the basic biology of human TH17 cells is necessary, including aspects of epigenetic regulation of the locus for IL-17 cytokines and other inflammatory mediators of this lymphocyte subset. Recently, it has been shown that human CD4^{pos}CD25^{high}CD27^{pos}CD45RA^{neg}Foxp3^{pos} regulatory T cells also possess an effector differentiation program resulting in IL-17 production (60).

The TH17 element adds complexity to the traditional concepts of immune regulation, but at the same time helps in the understanding of issues related to immune response such as cell differentiation, inflammatory response and its soluble mediators as well as specific prevailing gene patterns in each one of them. The ordination of cellular subsets into categories and families facilitates the understanding of inflammatory processes in different diseases and/or at different stages of chronic diseases.

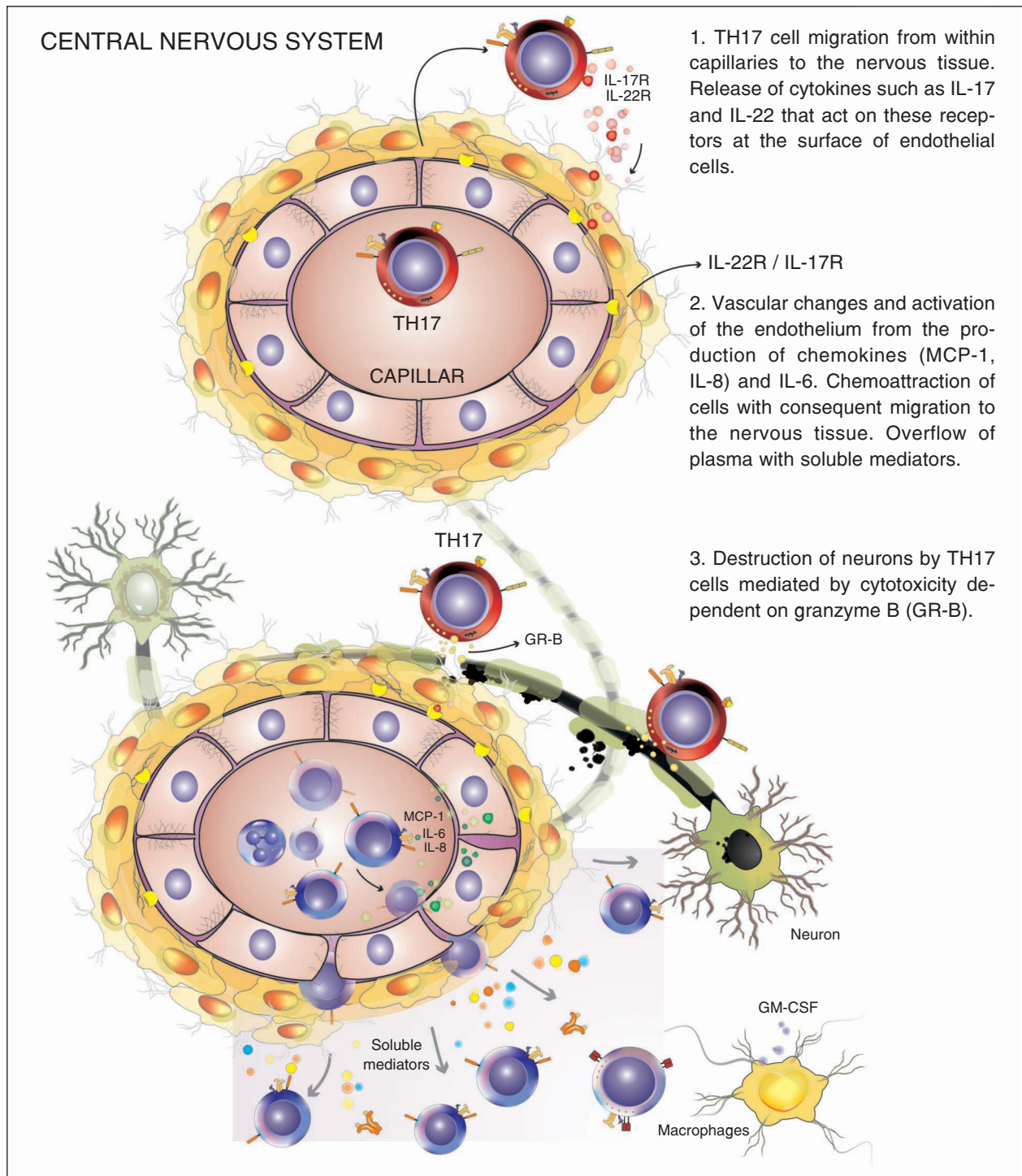


Figure 3. Schematic view of the participation of TH17 cells in the exacerbation of the inflammatory response in multiple sclerosis, mediated by the increase of the cells in nervous system tissue and release of inflammatory mediators in the brain. Action of cytokines released by TH17 on endothelial cells resulting in increased vascular permeability and production of chemokines (MCP-1, IL-8) and inflammatory cytokines such as IL-6. Participation of TH17 cells on the destruction of neurons is mediated by the release of granzyme B and activation of macrophages that start the production of cytokines such as granulocyte-macrophage colony-stimulating factor (GM-CSF). IL = interleukin; MCP-1 = monocyte chemoattractant protein-1.

The understanding of IL-17 regulatory pathways is necessary for a better comprehension of the pathophysiology of autoimmune diseases and shall contribute to the development of new opportunities for therapeutic intervention.

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