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Th17 cells: biology, pathogenesis of autoimmune and inflammatory diseases and therapeutic strategies

Mohan S Maddur^{1,2,3}, Pierre Miossec⁴, Srinivasa Kaveri^{1,2,3,5} and Jagadeesh Bayry^{1,2,3,5}

¹ INSERM, Unité 872, 15 rue de l'Ecole de Médecine, Paris, F-75006, France

² Centre de Recherche des Cordeliers, Equipe 16- Immunopathology and therapeutic immunointervention, Université Pierre et Marie Curie – Paris 6, UMR S 872, Paris, F-75006, France

³ Université Paris Descartes, UMR S 872 Paris, F-75006, France

⁴ Immunogenomics and Inflammation Research Unit, EA 4130, Department of Clinical Immunology and Rheumatology, Hôpital Edouard Herriot, University of Lyon, 69437 Lyon Cedex 03, France.

⁵ International Associated Laboratory IMPACT (Institut National de la Santé et de la Recherche Médicale, France - Indian Council of Medical Research, India), National Institute of Immunohaematology, Mumbai, India

Correspondence to: Jagadeesh Bayry, INSERM Unité 872, Equipe 16-Centre de Recherche des Cordeliers, 15 rue de l'Ecole de Médecine, Paris, F-75006, France.

Tel: 00 33 1 44 27 82 03/81 93 ; Fax: 00 33 1 44 27 81 94

E-mail: jagadeesh.bayry@crc.jussieu.fr

Abstract

Th17 cells that secrete cytokines IL-17A and IL-17F, and express lineage-specific transcription factor RORC (ROR γ t in mice) represent a distinct lineage of CD4⁺ T cells. TGF- β and inflammatory cytokines such as IL-6, IL-21, IL-1 β and IL-23 play a central role in the generation of Th17 cells. Th17 cells are critical for the clearance of extracellular pathogens including *Candida* and *Klebsiella*. However, under certain conditions, these cells and their effector molecules such as IL-17, IL-21, IL-22, GM-CSF and CCL20 are associated with the pathogenesis of several autoimmune and inflammatory diseases such as multiple sclerosis, rheumatoid arthritis, lupus, inflammatory bowel disease, allergy, asthma and psoriasis. Various therapeutic strategies are under investigation to target Th17 cells that include blocking the differentiation and amplification of Th17 cells, inhibiting or neutralizing the cytokines of Th17 cells and suppressing the transcription factors specific for Th17 cells. Since, Th17 cells display plasticity, therapeutic molecules that have broader specificities are promising candidates for clinical trials.

CD4⁺ T cells occupy central stage in the process of immune response by coordinating with different immune cells. Being effector cells, they are critical in generation, sustenance and regulation of immune response against pathogens as well as self-antigens. CD4⁺ T cells are heterogeneous and several subsets have been identified based on the distinct cytokine and transcription factor profiles. These subsets include Th1, Th2 and CD4⁺CD25⁺ regulatory T cells (Tregs). Although other T cell subsets such as TGF- β -producing Th3 cells, IL-10-secreting-T regulatory type 1, IL-9-producing Th9 cells and IL-22-producing Th22 cells have been described, their lineage-specific transcription factors have not been identified. More recently, Th17 cells that secrete cytokines IL-17A and IL-17F, and express surface IL-23 receptor (IL-23R) and lineage-specific transcription factor RORC (ROR γ t in mice) are identified as a distinct lineage of CD4⁺ T cells.¹⁻⁴ Although, Th17 cells share several surface markers of other CD4⁺ T cell subsets, recent results demonstrate that CCR6⁺CCR4⁺ or CCR2⁺CCR5⁻ memory CD4⁺ T cells are *bonafide* Th17 cells, indicating that Th17 population in the periphery are not homogenous.⁵⁻⁷ In addition, human Th17 cells specifically express lectin receptor CD161.^{6, 8} Th17 cells play a critical role in the clearance of extracellular pathogens including *Candida* and *Klebsiella*. However, under certain conditions, these cells can also be associated with the pathogenesis of various autoimmune and inflammatory diseases.

Biology of Th17 cells and regulation of their differentiation

In the periphery, naïve CD4⁺ T cells upon interaction with antigen presenting cells (APC) can undergo differentiation into distinct lineages under the influence of specific cytokines. Extensive studies in the past several years have contributed to in-depth understanding of the generation and function of Th17 cells.

Th17 differentiation in mouse

Several groups have convincingly shown that TGF- β and IL-6, two cytokines with opposing effects synergize to induce orphan nuclear receptor ROR γ t that orchestrates the expression of IL-17A and IL-17F in naïve T cells (Figure 1).²⁻⁴ IL-6 is a pro-inflammatory and pleiotropic cytokine secreted in high amounts by the innate cells, B and subsets of activated T cells. In addition, tumor cells, fibroblasts, endothelial cells and keratinocytes can also contribute to IL-6. Although, TGF- β is produced by multiple lineages of leukocytes and stromal cells, an autocrine or paracrine source of TGF- β is found to be important for Th17 differentiation *in vivo*.^{3, 9, 10} Thus, Treg-derived TGF- β enables differentiation of Th17 cells when naïve T cells are co-cultured with activated dendritic cells (DCs). Th17 cells can also express high amounts of TGF- β and this cytokine can act in an autocrine manner to maintain Th17 cells *in vivo*.¹⁰ Further, TNF- α and IL-1 β are found to enhance the TGF- β and IL-6-mediated differentiation of Th17 cells.²

Since, IL-6 knock-out mice are found to be susceptible to experimental autoimmune encephalomyelitis (EAE) upon depletion of Tregs, factors other than IL-6 are proposed to play a role in the induction of Th17 cells. Accordingly, TGF- β is found to synergize with IL-21 to induce ROR γ t and IL-17 in naïve T cells.^{11, 12} Since Th17 cells are the major producers of IL-21, an autocrine amplification loop is established by IL-21 to enhance their own differentiation.¹¹⁻¹³ It is also believed that in the absence of inflammation, when IL-6 levels are low, IL-21 produced by Th17, NK and NKT cells is important to maintain and to amplify the pool of Th17 precursors.^{11, 14} Thus, IL-21 has a major role in supporting Th17 cell-differentiation and tissue inflammation.

IL-23 is another inflammatory cytokine that contributes to Th17 generation. The combination of TGF- β and IL-6/IL-21 induces surface IL-23R on differentiating Th17 cells. Therefore, differentiating Th17 cells become responsive to activated myeloid cell-produced IL-23.^{4, 12, 13}

Notably, IL-23 (p19) deficiency is associated with the reduced number of Th17 cells *in vivo*. IL-23 is also required for the maintenance of Th17 cells *in vitro*, for the induction of tissue inflammation by *in vitro*-generated Th17 cells and for the Th17-mediated chronic inflammation *in vivo*.^{9, 15} Thus, IL-23 synergizes with IL-6 to enhance differentiation, survival and stabilization of Th17 cells.^{13, 15} Further, IL-23 can amplify Th17 cells by inducing pro-inflammatory cytokines such as IL-1 β , TNF- α and IL-6 in innate immune cells.¹⁴ Thus, complete Th17 cell differentiation was proposed to comprise three different stages. First, differentiation of Th17 cells triggered by the combined effect of TGF- β and IL-6/IL-21. Second, amplification of Th17 cells driven by IL-21 produced by Th17 cell themselves, probably with TGF- β . Third, stabilization of Th17 cells by IL-23.¹⁴

Despite these convincing findings on the requirement of cytokines (TGF- β /IL-6/IL-21/IL-23) for the Th17 differentiation in mice, the absolute requirement of TGF- β has been questioned in recent times. Th17 cells are present in the gut of TGF- β -signaling deficient mice.^{16, 17} In the T-bet and STAT6-deficient murine T cells, production of IL-17 could be induced by IL-6 alone in the absence of TGF- β .¹⁸ Further, IL-6 and IL-23 in combination with IL-1 β was able to induce IL-17 production in the absence of TGF- β -signaling,¹⁷ thus suggesting an alternate mode of Th17 cell differentiation. Th17 cells generated in the absence of TGF- β exhibit a phenotype of T-bet⁺ROR γ t⁺ and are pathogenic *in vivo*. However, this phenotype requires further validation as Th17 cells display profound instability as discussed later.

Th17 differentiation in human

Once the factors driving the differentiation of Th17 cells in mice are revealed convincingly, different cytokine combinations were examined to generate RORC-expressing human Th17 cells. Initially, it was argued that human Th17 differentiation is not dependent on TGF- β signaling, which is in contrast to mouse Th17 cells. It was proposed that the combination of

IL-1 β and IL-6/IL-23 or IL-23 alone could differentiate human Th17 cells from naïve T cells.^{19, 20} These results are biased, since differentiation of Th17 cells in these reports was performed using CD45RA⁺ Th cells purified from the peripheral blood. Also, the endogenous source of TGF- β (such as serum and platelets) was not carefully controlled in those reports. Subsequent studies done with serum-free medium and rigorously sorted naïve T cells solved these issues, establishing that similar to mouse, TGF- β is indispensable for the differentiation of human Th17 cells from naïve T cells.²¹⁻²³ Further, it is also believed that human Th17 cells can originate from a small subset of CD161⁺RORC⁺ precursors present in umbilical cord blood and thymus in response to combination of IL-23 and IL-1 β even in the complete absence of TGF- β .²⁴ In our opinion, this setting mimics an expansion of preexisting Th17 population rather than differentiation of *de novo* Th17 cells as discussed below.

TGF- β is essential for the induction of RORC in naïve T cells, although the expression and functions of RORC are inhibited at high concentrations of TGF- β .²² However, inflammatory cytokines such as IL-21, IL-1 β , IL-6 and IL-23 relieve the inhibition of RORC in CD4⁺ T cells and trigger the expression of IL-17 (Figure 1).²¹⁻²³ Essentially, naïve T cells do not express IL-1R and IL-23R. However, these receptors are induced following exposure to TGF- β and IL-6/IL-21 and making the cells receptive to IL-1 β and IL-23.^{21, 25} Further, it has been shown that the combination of TGF- β and IL-21 is sufficient to induce differentiation of human Th17 cells from naïve T cells and, IL-1 β and IL-6 are important to enhance the expansion of differentiated and memory Th17 cells.²¹ TGF- β can also favor human Th17 differentiation indirectly because of its suppressive activity on T-bet expression and consequently on the generation of Th1 cells.²⁶ Thus, cytokine requirements for driving the differentiation of Th17 cells are similar in both human and mouse.

Mechanistic pathways in the Th17 cell differentiation and expression of effector molecules

Differentiation of Th17 cells requires cooperative interaction of downstream molecules of TGF- β and IL-6 receptors-mediated signaling pathways (Figure 1). Basically, naïve T cells are receptive to IL-6 as these cells express functional IL-6 receptor. IL-6 receptor consists of inducible subunit IL-6R α and the constitutively expressed signaling subunit gp130. Although TCR-stimulation as well as IL-6-signaling down-regulates IL-6R α expression on naïve T cells, TGF- β can maintain the receptiveness of T cells to IL-6 by inducing the expression of IL-6 α . Binding of IL-6 to its receptor activates STAT3 but is transient due to induction of suppressor of cytokine signaling 3 (SOCS3).

STAT3 activation is necessary, but not sufficient for ROR γ t expression. TGF- β -signaling through its receptor (TGF β RI and TGF β RII complex) activates smad2 pathway leading to expression of both Foxp3 and ROR γ t.²⁷ Further, TGF- β -signaling through smad2/3 inhibits IL-6- and IL-21-induced SOCS3 expression, thus enhancing as well as prolonging the STAT3 activation in naïve T cells.^{16, 27} Hence, sustained activation of STAT3 in the presence of IL-6 and TGF- β relieves Foxp3-mediated suppression of ROR γ t, enhances ROR γ t expression and facilitates the Th17 transcriptional program. Smad-independent induction of Th17 cells by TGF- β has also been described. Thus, TGF- β can induce ROR γ t expression and Th17 cell differentiation by signaling through JNK-c-Jun pathway and by suppressing Eomesodermin (Eomes), a negative regulator of Th17 cells.²⁸

TGF- β and IL-6-induced STAT3 activation also induces the expression of another related nuclear receptor ROR α that synergizes with ROR γ t in Th17 cell differentiation. In cooperation with STAT3, both ROR γ t and ROR α bind to IL-17-promoter region leading to competent induction of IL-17A, IL-17F and IL-21.^{29, 30} In view of the similar and redundant role to that of ROR γ t, ROR α is believed to be a minor player in Th17 cell differentiation.

IL-23-signaling through IL-23R (induced by TGF- β and IL-6/IL-21) further enhances the activation of STAT3 that coordinates with ROR γ t to stabilize the Th17 cells and their function.³⁰ Further, IL-6-signaling enhances the expression of IL-1R on differentiating Th17 cells. IL-1 β act in synergy with IL-6 and IL-23 for the polarization of Th17 cells by regulating the expression of interferon regulatory factor 4 (IRF 4) that favors functional expression of ROR γ t.^{31, 32} Therefore, based on the activation state of T cells that are differentially receptive to various cytokine signals; the cytokines required for Th17 lineage commitment vary. This may explain the observed discrepancies in the Th17-cell differentiation models of initial studies.

In addition to the key regulators, other transcription factors such as Baft (member of AP-1 transcription factor family), I κ B ζ (nuclear I κ B family) and Runx1 (member of core binding factor- α) are also found to be essential for enhancing the Th17 differentiation and expression of effector molecules.³³⁻³⁵ Thus, Th17 differentiation appears to be governed by multiple cytokine signals and transcription factors.

Reciprocal regulation of Th17 and iTregs

In addition to natural Tregs (nTregs) that are thymic origin, Tregs can be induced (iTregs) in the periphery under specific conditions. Developmental pathways of Th17 cells and iTregs are closely related, reciprocally regulated and can influence the outcome of immune responses, particularly in autoimmune and inflammatory diseases.³⁶ TGF- β is the critical factor in common for Th17 cells and iTregs, since it is essential for inducing both ROR γ t and Foxp3. However, in the absence of inflammation, the prominent TGF- β alone induces Foxp3 leading to generation of iTregs that maintain immune tolerance along with nTregs. At molecular level, TGF- β -induced FoxP3 physically associates with ROR γ t and ROR α via Runx1. Through this interaction, FoxP3 antagonizes the expression and function of both

ROR γ t and ROR α leading to the inhibition of Th17 transcriptional program.^{35, 36} Accordingly, Foxp3⁺ROR γ t⁺ cells present in the small intestine produce less IL-17 compared to Foxp3⁻ROR γ t⁺ cells.³⁶ Following an inflammatory trigger, the pro-inflammatory cytokines IL-6/IL-21/IL-23 induce STAT3 that blocks TGF- β -driven Foxp3 expression to inhibit Tregs and exploits TGF- β signaling to enhance ROR γ t-expressing Th17 cells. Therefore, IL-6 and IL-21 have an important role in the reciprocal regulation of iTregs and Th17 cells by controlling the Foxp3/ROR γ t balance (Figure 1).^{3, 11, 13, 36, 37}

IL-2, a growth factor for Tregs, also fortifies cell-intrinsic reciprocal developmental relationship between Foxp3⁺ Tregs and Th17 cells. IL-2 induces phosphorylation of STAT5 and STAT5 can oppose Th17 differentiation by binding to *il17a* gene.³⁸ IL-2 can also inhibit Th17 cells via Ets-1, a member of the ETS family of transcription factors that negatively regulates Th17 differentiation.³⁹ Further, IL-2 decreases the expression of IL-6R, a key molecule implicated in Th17 polarization.⁴⁰

Retinoic acid, a vitamin A metabolite can reciprocally regulate Tregs and Th17 via TGF- β 1-dependent generation of Foxp3⁺ Tregs, even in the presence of IL-6.^{41, 42} Retinoic acid-induced Foxp3⁺ Tregs have a unique feature of high expression of gut homing receptors.⁴¹ Mechanistically, retinoic acid enhances TGF- β 1-driven Smad3 phosphorylation in naïve T cells possibly via nuclear retinoic acid receptor- α while inhibiting the up-regulation of IL-6R α subunit, IRF4 and IL-23R.⁴¹

The ligand-activated transcription factor aryl hydrocarbon receptor (AHR) can also exert reciprocal regulation of Treg- and Th17-cell differentiation in mice, a process however dependent on the ligands.⁴³ AHR activation by 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) induces functional Tregs, whereas 6-formylindolo[3,2-b]carbazole (FICZ) interferes with Treg-development and boosts Th17 cell differentiation in EAE.⁴³⁻⁴⁵ In contrast, in human T cells, AHR activation by TCDD induces Foxp3⁺ Tregs, whereas FICZ profoundly enhances

IL-22 production while decreasing the IL-23R and IL-17A in Th17 cells.⁴⁶ Therefore, AHR can be considered as an intriguing link between environmental toxins and immune equilibrium.

On contrary to the cell-intrinsic reciprocal regulation of Tregs and Th17 cells, recent studies have shown that Tregs complement Th17 cell-differentiation.^{2, 10, 47, 48} Tregs may serve as the source of TGF- β required for the induction of ROR γ t in Th17 cells.² Also, Tregs can promote early Th17 cell-differentiation through consumption of IL-2 that otherwise suppresses the Th17 cell programming by paracrine activation of STAT5.^{47, 48}

Relation between Th17 and Th1/Th2 cells

Th1 and Th2 cytokines, IFN- γ and IL-4 are known to inhibit the development of Th17 cells by paracrine as well as cell-intrinsic actions.¹ These effects are mediated by the mutual antagonism between the lineage-specific transcription factors.⁴⁹ IFN- γ enhances T-bet expression, which interacts with Runx1-ROR γ t complex to inhibit Th17 differentiation.⁴⁹ Further, IL-27 negatively regulates Th17 cells and promotes Th1 cell response in a STAT1-dependent manner and by inducing IL-10 in Th cells.⁵⁰⁻⁵²

IL-4-induced GATA3 might constrain the Th17 differentiation *in vitro* through IL-4-independent mechanisms, involving down-regulation of STAT3, NFATc2 and ROR γ t.⁵³ In view of the inhibitory effect of IFN- γ and IL-4 on Th17 cells, it is proposed that TGF- β -mediated repression of Th1/Th2 cells is critical for the Th17 differentiation. In contrast, Th17-related cytokines such as IL-23 and IL-17 are found to suppress mouse Th1 cell differentiation *in vitro* in the presence of exogenous IL-12.

Stability of Th17 cells

As compared to Th1/Th2/nTregs, Th17 cells display instability. Accordingly, in mice and humans, Th17 cells co-expressing IL-17/IFN- γ or ROR γ t/T-bet or FoxP3/IL-17/ROR γ t have been observed during inflammatory responses.^{5, 6, 17, 20, 36, 54} Recently, human circulating memory Th cells co-expressing IL-17A/IL-4 has also been identified.⁵⁵

The acquisition of a mixed phenotype by Th17 cells appears to be determined by the inflammatory environment (and hence cytokine milieu) as chronic inflammatory conditions such as EAE, can cause switch to alternative inflammatory cytokines in Th17 cells.⁵⁶ Surprisingly in this model, IL-23 that is considered to be stabilizing factor for the Th17 cell commitment was found to mediate the transformation of Th17 cells to produce IFN- γ and other inflammatory cytokines under chronic inflammatory conditions.⁵⁶ Further, IFN- γ can up-regulate IL-12R β 2 on Th17 cells and enhance their sensitivity to IL-12 resulting in Th17/Th1 phenotype that stably co-express ROR γ t and T-bet.⁵⁷ Interestingly, under inflammatory conditions in the gastrointestinal tract, Th17 cells can also acquire regulatory phenotype with immunosuppressive functions.⁵⁸ At molecular level, Th17 plasticity has been related to the bivalent epigenetic modification of histone proteins by methylation in the signature cytokine and key transcription factor genes.⁵⁹

Functions of effector molecules of Th17 cells

Th17 cells produce several effector molecules such as IL-17A, IL-17F, IL-21 and IL-22 (Figure 2). In addition, they also produce CCL20, GM-CSF, IL-8, IL-26 and IL-10, although many of these cytokines are not Th17-specific.

IL-17A is the prototype member of IL-17 family consisting of six cytokines- IL-17A, IL-17B, IL-17C, IL-17D, IL-17E (IL-25) and IL-17F. IL-17A and IL-17F have similar functions and are genetically linked. They are presumably expressed under the control of same locus and

hence are often co-expressed at the single cell level.¹⁴ Both IL-17A and IL-17F use IL-17 receptor A (IL-17RA)-IL-17RC heterodimer for their signalling although; IL-17A binds to IL-17RA with much higher affinity. Binding of IL-17 to its receptor recruits adaptor protein ACT1 that further stimulates TNF-receptor (TNFR)-associated factor 6 (TRAF6) to activate NF- κ B and MAPK pathways.¹⁴ Both IL-17A and IL-17F are key cytokines for the recruitment, activation and migration of neutrophils and can also target non-immune cells such as fibroblasts, endothelial, airway smooth muscle cells and epithelial cells to induce pro-inflammatory mediators IL-6, TNF- α , IL-1 β , GM-CSF, G-CSF, PGE2, nitric oxide, matrix-metalloproteinases and chemokines (CXCL1, CXCL8, CCL2, CCL7, CCL20).^{1, 14} IL-17 also regulates germinal-center formation and autoantibody production.

IL-22 belongs to IL-10 family of cytokines and is produced by terminally differentiated Th17 cells through IL-23-mediated STAT3 activation.¹⁴ AHR, a receptor for digoxin, plays an important role in the expression of IL-22.⁴⁴ The IL-22 receptor consists of a unique IL-22R1 chain and IL-10R2, and is highly expressed in epithelial cells and parenchymal tissues, but not on immune cells. Through this receptor complex, IL-22 activates STAT3 and MAPK pathways. IL-22 induces antimicrobial agents and β -defensins in keratinocytes and promotes epidermal hyperplasia. Therefore IL-22 is essential for the immune barrier function of epithelial cells.¹⁴

IL-21 is a member of IL-2 family of cytokines and mediates its functions via IL-21 receptor expressed mainly on B cells, but also on T cells and other myeloid cells.¹⁴ IL-21 receptor is a heterodimer of IL-21R and common cytokine-receptor γ chain (γ_c). Binding of IL-21 to its receptor complex activates JAK1 via IL-21R and JAK3 via γ_c leading to STAT3 activation. In addition to differentiation of Th17 cells, IL-21 stimulates (i) proliferation and differentiation of CD8⁺ T cells in combination with IL-7 or IL-15; (ii) B cell differentiation and antibody

class switching (IgG1, IgG3) by inducing Blimp-1 and Bcl-6; (iii) differentiation and cytotoxic program of NK and NKT cells and (iv) IL-8 production from DCs and MΦ.

CCL20 is a ligand for CCR6 expressed by DCs, B and subsets of T cells and has antimicrobial as well as chemoattractive activities. Th17 cells also express CCR6 and hence through CCL20 secretion, Th17 cells regulate their own recruitment to inflamed tissues. Further, CCL20 can be induced by IL-17 in the tissues indicating that CCL20 might have an important role in sustaining the Th17-mediated inflammation.

Th17 cells in autoimmune and inflammatory conditions

Th17 cells and their cytokines are associated with several autoimmune and inflammatory diseases, such as rheumatoid arthritis (RA), inflammatory bowel disease (IBD), systemic lupus erythematosus (SLE), multiple sclerosis (MS), allergy, asthma and psoriasis.^{60, 61}

Rheumatoid arthritis: The prevalence of IL-17⁺ and IL-22⁺ CD4⁺ cells is increased in the circulation of patients with RA and ankylosing spondylitis and these cells produce higher quantities of IL-17 following stimulation.⁶² IL-17 is also present at the sites of inflammatory arthritis and amplifies the inflammation induced by other cytokines and in particular TNF-α.

In collagen-induced arthritis (CIA) model, the disease is mainly mediated by IL-17, since IL-17 deficiency, or treatment with IL-17RA antagonist or with IL-17-neutralising antibody prior to disease onset attenuates arthritis with decreased joint damage and reduced serum IL-6.⁶³

IL-21 is up-regulated in the synovium, synovial fluid and in serum of early-stage RA patients and CIA mice and is correlated with the disease activity.⁶⁴ IL-21 regulates Th17 cells and promotes osteoclastogenesis in RA.⁶⁴ Further, inhibition of IL-21/IL-21 receptor pathway ameliorates arthritis in animal models.⁶⁵

IL-22 level in the serum of RA patients is associated with radiographic progression of the disease.^{66, 67} These findings are substantiated in experimental arthritis in mice wherein an

increased expression of IL-22 by synovial Th17 cells was observed during late stages of the disease.^{66, 67} Further, IL-22 can also promote osteoclastogenesis and regulate antibody production in arthritis.

In total, different effector molecules of Th17 cells synergize to enhance the disease activity in RA. However, recent study indicates transient phenotype nature of CD4⁺CD161⁺ Th17 cells in the synovial fluid of patients with RA and juvenile idiopathic arthritis.^{68, 69}

Systemic lupus erythematosus: SLE patients exhibit increased levels of IL-23, IL-21 and IL-17 as a result of expansion of Th17 cells. These changes are associated with the depleted Treg population and increased Th17/Th1 ratio.⁷⁰ Both in SLE patients and experimental models, IL-17 in coordination with IL-21 and BAFF promotes germinal centre formation and influences B cells to produce pathogenic autoantibodies.^{71, 72} The genetic association of SLE with polymorphisms of Th17-encoding molecules (such as IL-21)⁷³ or their receptors (like IL-21R) has been reported.⁷⁴ Also, genetic variants of transcription factors (such as ETS1) that negatively regulate Th17 differentiation can predispose to SLE.⁷⁵ Interestingly, blocking of IL-21 pathway ameliorates the autoimmune symptoms in the mouse model of SLE.⁷⁶

Multiple sclerosis: In MS patients, IL-17 expression is augmented in the blood and cerebrospinal fluid (CSF)-mononuclear cells and at the site of lesions.^{77, 78} Importantly, IL-17 expression is correlated with the disease activity. IL-17 and IL-22 promote blood-brain barrier (BBB) disruption and CNS inflammation by inducing chemokines in endothelial cells and by down-regulating tight junction proteins. IL-17 also stimulates astrocytes to produce ELR⁺ CXC-chemokines that eventually attract neutrophils to the BBB and activate them to release vasoactive substances.⁷⁹

Furthermore, IL-23 (but not IL-12) that expands IL-17-producing Th cells is critical for the induction of EAE. It has been shown that myelin antigen-specific Th17 cells directly interact with neuronal cells in the demyelinating lesions.^{80, 81} Of interest, either deficiency or

neutralization of IL-17 delays the onset of EAE and reduces the severity of disease.⁸⁰ A recent study further revealed that under chronic inflammatory conditions such as EAE, Th17 cells display plasticity. Thus, in the inflamed tissues, Th17 cells can switch from IL-17 to other inflammatory cytokines in particular IFN- γ .⁵⁶

Lately, two independent studies have identified the critical non-redundant role of Th17-produced GM-CSF in the pathogenesis of EAE. ROR γ t drives the production of GM-CSF in Th17 cells under the influence of IL-1- and IL-23-signaling. The GM-CSF in turn acts on APC (and in particular by CD103⁺ dermal DCs) to stimulate the secretion of IL-23 and activation of encephalitogenic T cells, setting a positive feedback loop during inflammation.⁸²⁻⁸⁴ In consensus, absence of GM-CSF conferred resistance to EAE in mice, even in the presence of IL-17 and/or IFN- γ .⁸²

Psoriasis: The psoriatic skin lesions are infiltrated by discrete populations of highly differentiated Th1 and Th17 lymphocytes.^{20, 85} IL-23, overproduced by dermal DCs and keratinocytes, stimulates Th17 cells within dermis to make elevated amounts of IL-17 as well as TNF- α , IL-22 and CCL20. These soluble mediators of Th17 cells might further enhance inflammation by their distinct actions. For example, CCL20 can attract CCR6⁺ cells to lesions and IL-17 can induce IL-6 and IL-8 in human skin keratinocytes.

Experimental model of psoriasis-like skin inflammation indicates that IL-22 plays a central role in the Th17 cell-mediated skin pathology.⁸⁶ In fact, IL-22 mRNA expression mirrored IL-17 in psoriatic skin. Interestingly, IL-22 mRNA expression returned to non-lesional levels upon treatment with cyclosporine, a conventional therapy for psoriasis.⁸⁵ Moreover, IL-22 also stimulates proliferation, abnormal differentiation, and migration of various epithelial cells *in vitro*.

Inflammatory bowel diseases: Crohn's disease (CD) and ulcerative colitis (UC) are the major but immunologically distinct forms of IBD in humans. CD-related inflammation is

characterized by a marked mucosal infiltration of T cells that secrete Th1 and Th17 cytokines. In UC, the local immune response is less polarized but may show enhanced production of IL-5, IL-13 and Th17 cytokines.⁸⁷

In general, Th17 cells are considered to be more potent than Th1 cells in transferring IBD.⁸⁷ Elevated levels of IL-17A, IL-17F and IL-21 are observed in the sera of patients with active IBD.⁸⁷ Colitic mice show an increased number of Th17 cells in the inflamed areas of lamina propria of ileum and colon. IL-21 can mediate Th17 differentiation and enhance inflammatory responses by recruiting T cells to the inflamed gut and by eliciting the secretion of matrix-degrading enzymes by gut fibroblasts. In addition, genetic studies have identified alleles of *il-23r* (amongst others) and their association with either predisposition or protection from IBD.⁸⁷

In contrast to other Th17-cytokines, IL-22 was however found to be protective in IBD through maintaining the integrity of the epithelial barrier and protecting mucin-secreting goblet cells.⁸⁸ Thus, Th17 cytokines have differential effects on the course and pathogenesis of IBD and the net effect of these cytokines possibly depend on their relative abundance.

Allergy and asthma: IL-17 mediates recruitment of neutrophils and can also activate airway smooth muscle cells and epithelial cells to induce pro-inflammatory mediators. In addition, IL-23 and Th17 cells can also up-regulate Th2-cell-mediated eosinophilic airway inflammation.^{1, 14} Therefore, in addition to Th2 cells that are traditionally considered as pathogenic in allergy and asthma, Th17 cells can also play a key role in the airway inflammation.

In asthmatic patients, IL-17A/F expression is increased in the lungs, sputum, bronchoalveolar lavage fluids and/or sera, and is correlated with the severity of airway hypersensitivity.⁶¹ The number of Th17 cells and the expression of RORC were also enhanced in the peripheral blood

of asthmatic patients and these cells produced high amounts of Th17 cytokines upon *ex vivo* activation.

A recent report demonstrates that Th17 cells show plasticity in asthma condition wherein patients display CCR6⁺CD161⁺CD4⁺ T cells that co-express IL-17A/IL-4 in the circulation.⁵⁵ It was found that memory Th17 cells express IL-4R and are responsive to IL-4 that induces STAT6 phosphorylation.⁵⁵ Thus, this report suggests a vicious interplay of Th2 and Th17 cells wherein IL-4-rich environment created by Th2 cells (along with other cells such as basophils) can provoke plasticity in Th17 cells and generate Th17/Th2 phenotype that might further aggravate the disease.

IL-17A can play a role in the pathogenesis of asthma and allergy via modulation of the expression of glucocorticoid receptors (GR). Due to alternative splicing of the GR pre-mRNA, GRs are expressed in two highly homologous isoforms: GR α and GR β . GR α is a ligand-activated transcription factor that mediates the expression of glucocorticoid-responsive genes. GR β is transcriptionally inactive and does not bind glucocorticoids. However, GR β can act as endogenous inhibitor of glucocorticoid functions. It was found that IL-17A enhances the expression of GR β and hence may cause steroid unresponsiveness or resistance in patients.⁸⁹ Furthermore, IL-17A can mediate allergic reactions by promoting IgE class switch recombination in B cells by stimulating ϵ germ-line transcripts (ϵ GLTs).^{61, 90}

Strategies to target Th17 cells and their cytokines

Th17 cells exhibit diverse therapeutic targets. The possible therapeutic strategies are (i) blocking the differentiation and amplification of Th17 cells (ii) inhibiting or neutralizing the cytokines of Th17 cells and (iii) inhibiting the transcription factors specific for Th17 cells

(i) Blocking the differentiation and amplification of Th17 cells. Innate immune cells and their inflammatory cytokines such as IL-21, IL-23, IL-6 and IL-1 β play a critical role in

driving the differentiation and amplification of Th17 cells. Therefore, suppression of APCs such as DCs and macrophages or inhibition of their inflammatory cytokines by neutralizing monoclonal antibodies or blocking the receptors for inflammatory cytokines are expected to inhibit T cell responses including Th17.⁹¹⁻⁹³ Such strategies can also reciprocally regulate Tregs and Th17 populations.^{93, 94} Of interest, blockade of IL-21/IL-21 receptor pathway by IL-21R.Fc ameliorates clinical and histologic signs of CIA.⁶⁵ Although targeting IL-21R is specific for Th17 cells, other targets are not specific for Th17 cells as innate inflammatory cytokines have diverse and redundant functions.

Additional molecules explored for inhibition of Th17 differentiation *in vitro* and *in vivo* in EAE model include: AM-80, a synthetic retinoid that binds to the retinoic acid-binding site of retinoic acid receptors; and halofuginone, a derivative of plant alkaloid febrifuge that activates amino acid starvation response.^{95, 96}

Ustekinumab, a human monoclonal antibody that targets IL-12/IL-23 pathway by binding to common p40 subunit has shown promise for the treatment of psoriasis and CD.^{97, 98} The success of ustekinumab in these diseases can be explained by the fact that both Th1 and Th17 cell are implicated in the pathogenesis of psoriasis and CD and that ustekinumab can inhibit both T cell populations by inhibiting IL-12 and IL-23.

(ii) Inhibiting or neutralizing the cytokines of Th17 cells: The specific targets include IL-17A/F and IL-21 and less specific targets are IL-22, GM-CSF and CCL20.

1,25-dihydroxyvitamin D3 ameliorates Th17 autoimmunity via transcriptional modulation of IL-17A while reciprocally inducing Foxp3.⁹⁹ N-acetylglucosamine inhibits both Th1/ Th17 responses and inhibits MOG-induced EAE by inhibiting the secretion of IFN- γ , TNF- α , IL-17 and IL-22.¹⁰⁰

Recently, the efficacy and safety of neutralizing humanized anti-IL-17A MAbs AIN457 and LY2439821 have been investigated. AIN457 induced clinically relevant responses of variable magnitude in RA, psoriasis and uveitis patients.¹⁰¹ Similarly, LY2439821 MAb used in combination with oral disease-modifying anti-rheumatic drugs, improved clinical signs and symptoms of RA, with no strong adverse effects.¹⁰² Further randomized clinical trials are required to confirm the benefits of anti-IL-17 MAbs in RA and other diseases.

(iii) Inhibition of transcription factors specific for Th17 cells: Here the targets include ROR γ t/RORC and STAT3 that govern Th17 polarization and functions.

The nuclear receptor peroxisome proliferator-activated receptor gamma (PPAR γ) agonist, pioglitazone inhibits human and murine Th17 differentiation by reducing the TGF- β /IL-6-induced expression of ROR γ t/RORC.¹⁰³ This inhibition of ROR γ t is associated with suppression of the development of CNS autoimmunity.¹⁰³ Simvastatin, a cholesterol-lowering agent with immunomodulatory features, inhibits IL-17 by targeting multiple IL-17-regulatory cytokines and by suppressing the expression of RORC in human Th cells.¹⁰⁴ More recently, cardiac glycoside digoxin has been shown to specifically suppress murine and human Th17 cell differentiation by antagonizing ROR γ t/RORC activity and is effective in delaying the onset and reducing the severity of EAE.¹⁰⁵

Zinc, an essential trace element required for maintenance of structure and activity of enzymes and transcription factors, suppresses Th17 cells by inhibiting STAT3 activation and is protective in EAE and CIA.¹⁰⁶ Further, platelet-activating factor receptor antagonist PCA-4248 suppresses psoriasis-like skin disease in experimental models by inhibiting the cytokines of Th1/Th17 cells and Th17-specific transcription factor STAT3.¹⁰⁷ Recently, leukemia inhibitory factor produced by neural progenitor cell is shown to ameliorate EAE via

interference with IL-6-induced STAT3 phosphorylation required for Th17 cell differentiation, while activating a signaling cascade that involves ERK and SOCS3.¹⁰⁸

In addition, certain therapeutic molecules can act broadly on pathogenic T cells including Th17 cells. Intravenous immunoglobulin (IVIg), a therapeutic preparation of normal IgG obtained from pooled plasma of thousands of healthy donors, inhibits both differentiation and expansion of Th17 cells and suppresses Th17 cytokines IL-17A, IL-21, IL-22 and CCL20.^{109,}

¹¹⁰ This inhibition by IVIg was associated with suppression of both RORC and STAT3. Of interest, the inhibition of Th17 expansion was associated with a reciprocal regulation of Tregs.^{109, 110} These novel mechanisms of IVIg might explain its therapeutic efficacy in autoimmune diseases such as Kawasaki disease, dermatomyositis and vasculitis where Th17 cells play an important role in the pathogenesis.¹¹¹ Further, by enhancing the affinity of glucocorticoid receptors, IVIg might also overcome IL-17A-mediated steroid unresponsiveness or resistance.^{89, 112}

Rapamycin, an immunosuppressive drug, promotes *in vitro* expansion of nTregs by inhibition of effector T cells including Th17 cells.¹¹³ These effects of rapamycin are mediated by inhibition of mTOR pathway.

Conclusion and perspectives

Th17 cells display considerable plasticity. In addition to IL-17⁺ cells, Th17 cells with mixed phenotype are also observed in the peripheral blood and in inflamed tissues. These findings imply that Th17 cells are not stable and depending on the type of inflammation and cytokine milieu, Th17 cells can acquire a phenotype of other T cell subsets such as IL-17⁺IFN γ ⁺ T cells and IL17⁺IL-4⁺ T cells. Based on a recent data obtained by IL-17A fate-reporter mice,⁵⁶ Th17 cells appear to be stable under acute inflammation while under chronic inflammation, these cells are vulnerable to get a mixed phenotype. Therefore, detailed investigations are required

to confirm whether Th1- or Th2-mediated autoimmune and inflammatory diseases are *per se* caused by Th1 or Th2 cells or by those ex-Th17 cells that are converted into Th1 or Th2 phenotype.

The instability of Th17 cells poses additional problem for isolating these cellular populations from the circulation and from the inflamed tissues. Although a combination of chemokine receptors and CD161 was used to isolate Th17 cells, it is not yet known whether these isolated cells are stable or if this population contains mixture population. By using CCR6, CCR4, CCR2 and CD161 markers as scaffold, further classification of Th17 cell subsets can be performed.

Several Th17-specific therapeutic strategies are under investigation. Although Th17 cells and their cytokines are associated with several autoimmune and inflammatory diseases, it is important to underline that in most of these diseases, the pathogenic role of Th17 cells is not formally demonstrated. Furthermore, other CD4⁺ T cell subsets are also implicated in the pathogenesis of many of the Th17-associated diseases including psoriasis, IBD, SLE and asthma. Therefore, in these diseases, therapies that target Th17 alone may not confer complete remission. Of interest, several therapeutic molecules that have shown encouraging results in experimental models have broader specificities and hence are promising candidates for clinical trials.

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Figure Legends

Figure 1. Mechanisms of induction of Th17 cells. TGF- β is essential for the generation of both induced regulatory T cells (iTreg) and Th17 cells via induction of FoxP3 and RORC. But in the absence of inflammation, FoxP3 represses RORC and promotes iTregs. Signaling via inflammatory cytokines such as IL-6, IL-21 and IL-23 results in STAT3 phosphorylation, relieves RORC from the suppression of FoxP3 and initiate Th17 programming. STAT3 in combination with IFN regulatory factor 4 (IRF4) further induces RORC expression. The transcription factors STAT3, RORC and Runx1 bind to the promoter regions of *il17*, *il21*, *il22* and *ccl20* genes and induce IL-17, IL-21, IL-22 and CCL20. The Th17 programming can be antagonized by cytokines such as IFN- γ , IL-2 and IL-27. IL-2 and IL-27-mediated activation of STAT5 and STAT1 inhibit STAT3, while T-bet induced by IFN- γ can block RORC.

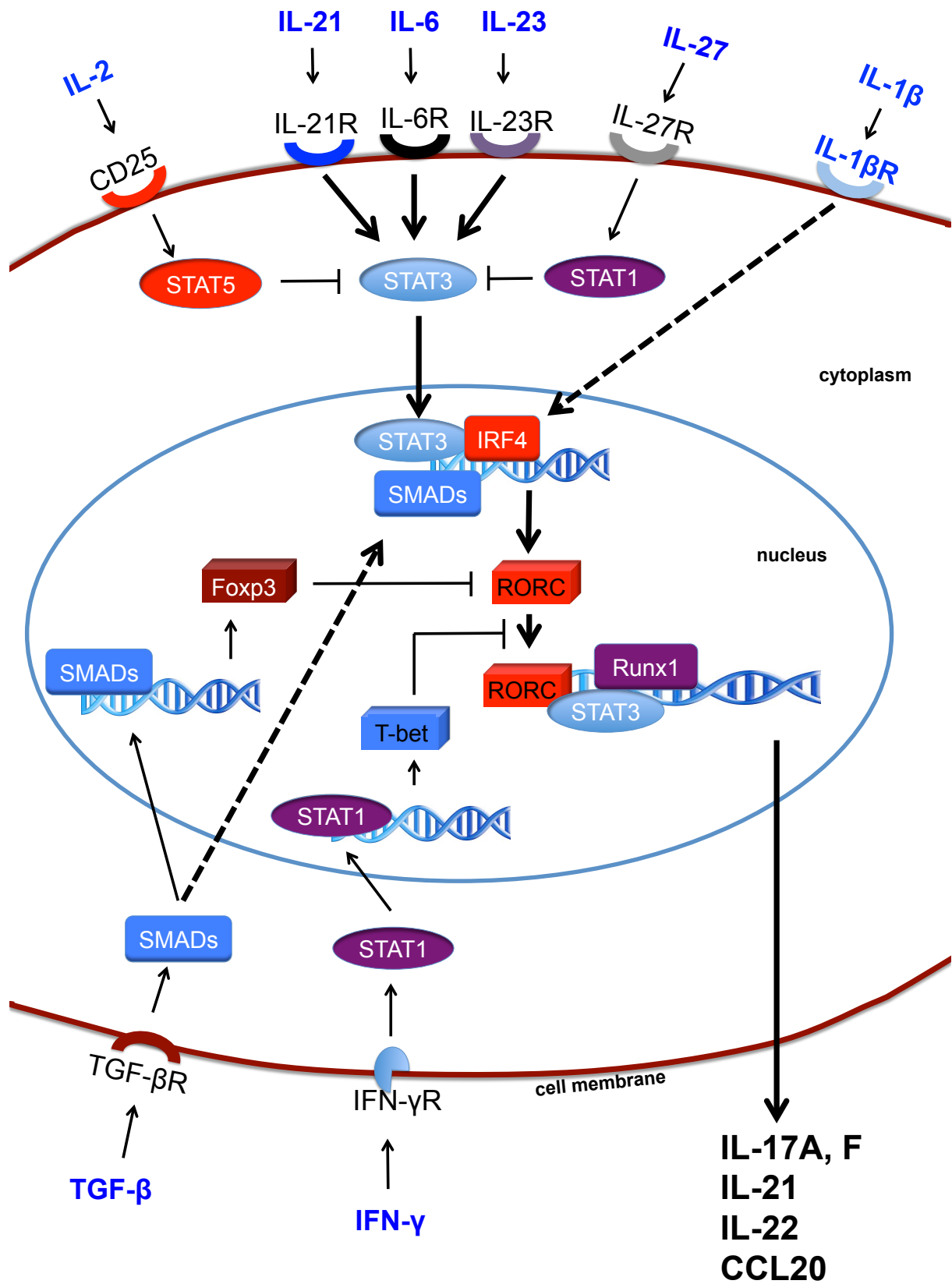


Figure 2. Functions of Th17 cytokines and chemokines. Th17 cells secrete several effector molecules including IL-21, IL-22, IL-17A/F and CCL20. These soluble factors act on both immune and nonimmune cells and mediate several functions such as differentiation of cells, release of anti-microbial molecules, cytokines and chemokines, and recruitment of cells to the site of inflammation. Abbreviations: B, B cell; CD8, cytotoxic T cell; NK, natural killer cell; EpC, epithelial cell; HC, hepatic cell; EC, endothelial cell; FB, fibroblast; MØ, macrophage, DC, dendritic cell; NØ, neutrophil; T, T cell.

